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Effect of Workplace Chemicals on Reproductive Function in Laboratory Animals, Joseph Santodonato, Life and Environmental Sciences Division, Syracuse Research Corporation, Syracuse,, New York.

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REPRODUCTIVE HAZARDS OF CHEMICAL EXPOSURES IN THE WORKPLACE

(also listed as *Chemical Hazards to Human Reproduction in the Workplace*)

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INTRODUCTION

The purpose of this report is to review the scientific literature concerning reproductive effects of chemicals found in the workplace. The emphasis of the review is on human reproduction. Examples of findings from animal studies are outlined at the end of the review. For chemicals with limited information on human reproductive hazards, a summary of animal findings is included in the text.

The majority of the studies presented focus on workplace exposures; however, studies arising from environmental exposures, accidental poisonings, or case studies are also included. The latter studies are presented to elucidate potential reproductive hazards of these chemicals in the workplace.

For each major chemical, we briefly describe the major occupations where exposures have occurred and we review the major findings including the study designs, exposure data when available, and major outcomes. Each chemical is divided into 3 main sections: mutagenicity, male exposure, and female exposure. We state when no relevant information has been found for either male or for female exposures. Although most of the studies reviewed in the mutagenicity sections examined chemical effects on somatic tissue, these effects may be reflective of their hazard to the chromosomal makeup of reproductive cells. Chemicals which are mutagens may also be teratogens and thereby, play a role in the etiology of congenital malformations or spontaneous abortions.

For male exposures, we review the following outcomes: semen quality, infertility, potency and libido, physiologic changes, reproductive outcome of female partner, neonatal health (birthweight, congenital malformations), infant mortality, and neurodevelopment. For female exposures, we include menstrual disorders, infertility, placental transfer, breastmilk, pregnancy complications, pregnancy outcome (spontaneous abortions, stillbirths, sex ratio), neonatal health (birthweight, congenital malformations), infant mortality, and neurodevelopment. The comment section at the end of each major section provides a summary of effects and a short critique of the literature.

Studies which are included in the Industry section at the end of the document, are those where the specific exposures were not clearly stated. Often exposures can be inferred. Finally, all studies relating to transplacental carcinogenesis are included in one section, because few studies have examined this outcome and because mostly parental occupations rather then their specific exposures were implicated.

We note that a few of the chemicals reviewed here are no longer available in the United States. Some continue to pose a health threat because of their endurance in the ecosystem or because of their long biological half-life in human tissue. Others are included because they may provide insight into hazards of chemicals which have similar chemical properties or structures.

ANESTHETIC AGENTS

At room temperature, anesthetic agents are either gases or volatile liquids (Vainio, 1982). Traces of anesthetics present a potential occupational health hazard when small concentrations of these gases and vapors leak from the anesthetic breathing circuit. An estimated 214,000 medical personnel including surgeons, anesthesiologists, nurse anesthetists, operating room nurses and technicians, dentists, laboratory personnel, and veterinarians are exposed to anesthetic agents (NIOSH Criteria Document,1977).

The most widely used anesthetic gas is nitrous oxide (Vainio,1982). Other commonly used agents include halothane, enflurane methoxyflurane,and cyclopropane. The fluorinated hydrocarbons replaced diethyl ether and chloroform which were used commonly as anesthetics until 1950 (NIOSH Criteria Document, 1977). Levels of waste anesthetics in ambient air depend on the anesthetic technique, scavenging devices and ventilation systems (Vainio, 1982). In poorly ventilated rooms levels of halothane can build up to 400 ppm and levels of nitrous oxide up to 8000 ppm (Green, 1981).

While dentists tend to administer nitrous oxide alone, physicians primarily use nitrous oxide combined with the halogenated agents, making the effect of any one agent difficult to document (Cohen et al., 1980).

Male Exposure

Semen quality. Only one study has investigated the effect of exposure to anesthetics on sperm morphology and concentration. Wyrobek and his associates (1981) found that the concentration of sperm and the percentage of abnormally-shaped sperm of anesthesiologists exposed to nitrous oxide did not differ significantly from a control group of beginning medical residents. The trace amounts of nitrous oxide sampled in the three hospitals where semen samples were collected ranged from 5-500 ppm with a mean concentration of less than 50 ppm.

Infertility. Male infertility, although investigated, has not been found to be a significant problem for men working with anesthetic agents. Knill-Jones and coworkers' (1972) investigation of infertility in anesthetists, and in hospital and non-hospital doctors unexposed to anesthetics, revealed no diffferences between the groups. Another British study indicated that infertility was a common, but not statistically significant complaint of anesthetists (Tomlin 1979). Neither study indicated how fertility was defined or measured.

Pregnancy outcome of female partner: Spontaneous abortion. A number of studies have examined the frequency of spontaneous abortions among the female partners of men exposed to anesthetic gases. One of the earliest investigations of the reproductive hazards of inhalation anesthetics revealed twice as many spontaneous abortions among wives of practicing male anesthetists in Denmark (Askrog and Harvald 1970). Subsequent studies in the U.S. (American Society of Anesthesiologists (ASA) 1974; Spence et al., 1977, Cohen et al., 1975; 1980) have also examined the frequency of spontaneous abortion in wives of exposed dentists and operating room personnel. Of these, one study has indicated rates that differ significantly from control group wives (Cohen et al., 1980). A 50% increase in the incidence of spontaneous abortion was noted in wives of male dentists "heavily exposed" (in excess of 8 hours/week) to nitrous oxide and halogenated agents prior to the year of conception. When the group exposed only to nitrous oxide was analyzed by itself, a similar increase in spontaneous abortion was apparent. An analysis of the group exposed to halogenated agents alone was too small to assure statistical reliability. Cohen et al. did not specify concentrations of any of the agents. The authors suggest that the increased frequency of spontaneous abortion with paternal exposure occurs through sperm or semen transmission. No other hypothesis was put forth.

Pregnancy outcome of female partner:sex ratio among offspring. Three investigations (Askrog and Harvald, 1970; Wyatt, 1973; Mirakhur and Badve, 1975) noted a decrease in the number of male children born to wives of exposed anesthetists. Wyatt (1973), the only investigator whose finding was significant, compared the sex ratio of the children of anesthetists to the general population of England and Wales. Of the children admitted to the study, 56.8% were girls.

Neonatal health: Congenital malformation. The findings on congenital malformations in children of exposed men are inconsistent. A number of studies examined this outcome (ASA, 1974; Mirakhur and Badve, 1975; Knill-Jones et al., 1975; Cohen et al., 1975; Spence et al., 1977; Cohen et al., 1980), although only two studies demonstrate a statistically significant increase. Spence et al. (1977) whose analysis combine data from three previously retrospective studies (Knill-Jones et al., 1972, Cohen et al., 1974, Knill-Jones et al.,1975) found a 5.0% rate of abnormalities in children of male anesthetists compared to a rate of 3.7% in control children. In the ASA study (1984) there was a 25% increase in the incidence of unspecified defects for exposed male anesthesiologists compared with unexposed males. Knill-Jones and associates showed an elevated frequency of a group of minor defects but not of major malformations in children of exposed male anesthetists in England.

Neurodevelopment An Indian survey (Mirakur and Badve,1975) reported delayed developmental milestones in 23 of the children of male physicians exposed to anesthetics. In contrast, one child of the control physicians demonstrated a lag. This difference was statistically significant, although the data was not adjusted for age, parity or other confounders. The authors note that ether is the volatile agent most commonly at the time of study.

Female Exposure

Infertility. Knill-Jones and associates (1972) revealed a significant difference in infertility of no known cause among practicing female anesthetists (12%) as compared with female physician controls (6%) in

England by Knill-Jones et al. (1972). Of the 65 anesthetists reporting this problem, 36 (44%) conceived after an unspecified period of infertility, with 33 (92%) of these employed as anesthetists at the onset of their pregnancy. This implies that other factors, apart from or in addition to anesthetic agents may be responsible for the infertility.

Menstrual disorders. Rosenberg and Kirves (1973) reported that Finnish nurse anesthetists compared with four other types of nurses had the highest frequency of unspecified menstrual irregularities (17%). Intensive care nurses followed close behind (16.5%). These figures are not significant, but indicate that certain environmental conditions as well as anesthetic agents may be implicated with menstrual disorders.

Pregnancy complications. One study observed that a high percentage of operating room nurses reported nausea during their pregnancies as compared with general duty nurses (Cohen et al.,1971). The investigators suggested nausea indicated successful implantation, but also noted that other investigators had found that nausea resulted from prolonged exposure to certain anesthetics (Whitcher et al., 1977, cited by Cohen et al.,1971). Thus, it is unclear whether nausea is related to exposure to anesthesia or to pregnancy itself.

In an Indian study, the incidence of Cesarean section was 30.3% for anesthetists compared to 15.8% for other physicians. (Mirakhur and Badve, 1975). The authors suggested that increased numbers of Cesarean deliveries may reflect a higher incidence of toxemia or accidental hemmorrhages, or that anesthetists, because they work closely with obstetrical colleagues, choose to have Cesarians more often.

Pregnancy outcome: Spontaneous abortion. A number of studies have revealed significant increases in the number of spontaneous abortions among women exposed to anesthetic agents. (Vaisman, 1968; Askrog and Harvald, 1970; Cohen et al., 1971; Knill-Jones et al., 1972; Rosenberg and Kirves, 1973; ASA, 1974; Knill-Jones et al., 1975; Mirakhur and Badve, 1975; Spence et al., 1977; Tomlin, 1979; Cohen et al., 1980). How investigators define "exposed" varies by study. For example, Tomlin (1979) defines exposure by occupation, i.e. anesthesiologist. On the other hand,in the ASA study (1974) exposure is based on working with anesthetics during the first trimester of pregnancy and one year previous. All of the studies were conducted using postal questionnaires, and have examined the pregnancy outcome of anesthetic physicians, operating room nurses and technicians, dentists and dental assistants. Rates of spontaneous abortion in these exposed groups of women range from 14.2% to 38%. Control group rates range from 5.9% to 15.1%. In contrast to these findings, three studies examining spontaneous abortion as an outcome for women working with anesthetic agents showed no significant increase as compared to control group (Pharoah et al., 1972, Rosenberg and Vanttinen, 1978; Axelsson and Rylander, 1982). The two most recent studies validated their data with hospital medical records.

Several studies have indicated that spontaneous abortion occurs at an earlier point in time among women occupationally-exposed to anesthetics as compared to their controls. (Cohen et al., 1971; Rosenberg and Kirves 1973; Rosenberg and Vanttinen, 1978) The ASA study (1974), however, does not support this finding.

Pregnancy outcome: Stillbirths The possible increase in stillbirths and perinatal deaths among women exposed to anesthetic agents has been questioned in a number of studies investigating pregnancy outcome. (Askrog and Harvald, 1970; Knill-Jones et al., 1972; Mirakhur and Badve, 1975; Knill-Jones et al., 1975; Pharoah et al., 1977; Ericson and Kallen, 1979) Although slight increases have been reported, there were no significant differences found when rates were compared to control groups.

Pregnancy outcome: Sex ratio among offspring. No significant alterations in the male:female sex ratio of the children were demonstrated in four studies that examined this outcome (Cohen et al., 1971;Knill-Jones et al., 1972; ASA, 1974; Mirakhur and Badve, 1975). In fact, Mirakhur and Badve (1975) found a "preponderance of male babies" (60.5% to 39.5%) among practicing female anesthetists that could not be explained.

Neonatal health: Congenital malformations. A number of studies have reported an increased frequency of congenital malformations among offspring of women exposed to anesthetic agents (Askrog and Harvald, 1970; Corbett et al., 1974; ASA, 1974; Knill-Jones et al., 1975; Pharoah et al., 1977; Tomlin, 1979; Cohen et al., 1980). In three studies, musculoskeletal abnormalities were reported as a common malformation

(Pharoah, 1977; Tomlin, 1979; Cohen et al., 1980). Such defects as hemangiomas, inguinal hernias, and CNS defects were also found. Other studies, however, have reported no significant difference in congenital malformations among female anesthetic staff when compared to non-anesthetist staff (Rosenberg and Kirves, 1973; Knill-Jones et al., 1975; Spence et al., 1977; Ericson and Kallen, 1979). In many studies, anomalies are often not well-defined, and multiple defects in one child may be double counted.

Neonatal health: Birth weight. Low birth weight (2500 grams or less) has been reported in children of women exposed to anesthetic agents during pregnancy (Rosenberg and Kirves, 1973; Pharoah et al., 1977; Rosenberg and Vanttinen 1978; Tomlin, 1979). Tomlin noted that girls, who had birthweights 15% lower than expected, were more affected by their mothers' exposure than boys. Overall, no differences were deemed statistically significant.

Neurodevelopment. A British study (Tomlin, 1979) found that children of anesthetists were more likely to have difficulties in intellectual development and communication of the "dyslexic pattern." The author suggests that the neurodevelopmental performance in children exposed in-utero exposure to anesthetic agents warrants further investigation. His study describes several case studies, and presents data that is not tested for significance.

Comments

There are no definitive findings on the reproductive effects of anesthetic agents. There are, however, trends toward several undesirable outcomes; an increase in the frequency of spontaneous abortions among women who work in areas where anesthetics are used, and an increase in congenital malformations. In female partners of men exposed to the agents there is less evidence of an association for either outcome, though some studies have revealed positive findings. Of other adverse outcomes discussed, such as low birth weigh and neurodevelopmental effects, findings are limited by a lack of data.

The various epidemiologic investigations reviewed here are difficult to compare and to validate because they lack information on agents used and exposure quantification. For the majority of the studies "exposure" is defined by occupation, e.g., operating room nurse, dentist, anesthesiologist, and/or by years working with anesthetic agents. Furthermore, few studies have discussed the sorts of scavenging devices or ventilation systems, or lack thereof, operating within the workplace.

There are also general methodological problems worth noting that run across many of the studies. Several of these have been the basis of the reviews by outside authors writing on the current research. (Vessey, 1978; Vessey and Nunn, 1980; Edling 1980; Ferstandig, 1982). They point out the pitfalls of the retrospective design and the use of postal questionnaires, the primary source of data for most studies. A common criticism is the candidness of the questionnaires; they were often "loaded," so as to encourage reporting bias. For example, the ASA study (1984) entitled its questionnaire "effects of waste anesthetics on health. With the exception of two Swedish studies (Ericson and Kallen, 1979; Axelsson and Rylander, 1982) who validated their data with information from medical registries, the other studies relied solely on data collected from personal questionnaires. Neither of the Swedish studies revealed positive findings. In addition, a poor and uneven response rate, failure to choose the proper control group, and failure to adjust for basic confounding factors were problems acknowledged frequently by those reviewing the epidemiologic literature.

Interestingly, many investigators have cautioned readers against making a cause and effect relationship between exposure to anesthetic agents and the reproductive outcome under study. In addition to speculating on anesthetic agents, they put forth other factors that may be responsible for an adverse outcome: 1) physical factors such as increased physical activity, and irregular and excessive work schedules; 2) psychological factors such as nervous and emotion tension, stress, and prolonged concentration; 3) environmental factors that medical personnel often encounter including sprays and solvent vapors, transmissable viruses, radiation (Vaisman, 1967, cited by Ferstandig, 1982; Cohen et al., 1971, Corbett et al., 1974). Therefore, although anesthetic agents may indeed be responsible for outcomes like spontaneous abortion or congenital malformations, additional factors may contribute to their effect.

While waste anesthetics may not be totally eliminated through proper ventilation and scavenging systems, levels may at least be reduced. Adverse reproductive effects may be substantially curtailed by the advent and use of more advanced systems. Further epidemiologic investigations should examine the ventiliation and scavenging systems to determine if anesthetic agents continue to pose a reproductive hazard.

CHEMICAL STERILIZING AGENTS

It has been estimated that more than 100,000 people are employed in the chemical sterization of medical instruments, pharmaceuticals, and foodstuffs (Hemminki et al.,1982). Sterilization, which aims to destroy microbial life, involves such liquids and gases as ethylene oxide, formaldehyde, propylene oxide, and glutaraldehyde (Vainio, 1982). This section examines the use of ethylene oxide and formaldehyde, both implicated in causing adverse reproductive health effects.

Ethylene Oxide

Ethylene oxide, or ETO, is a compound derived from the oxidation of ethylene in the presence of a silver catalyst (Patty's,1981) It is used in the manufacture of higher alcohol, petroleum, and as a fumigant in foodstuffs. It is one of the top U.S. chemicals by volume (Glaser, 1982). A colorless gas, it is probably most well known for its use as a sterilant of equipment and supplies in health care facilities (Hansen, et al. 1984). NIOSH estimates that 75,000 workers are potentially exposed to ETO in medical facilities alone (NIOSH 1979, cited by Glaser). The finding that ETO has mutagenic potential in nonmammalian and mammalian systems has prompted OSHA's reevaluation of the exposure standard and reappraisal of its use in health care (Wolman, 1982).

Animal Studies

Mutagenic effects of ethylene oxide have been demonstrated in vitro and in vivo. Regarding reproductive effects, in both male and female rats decreased fertility and litter size have been reported. In a single study when ethylene oxide was administered intravenously to female rats, fetal death and fetal malformations were observed. Doses were also toxic to the dam. Overall, there have been a limited number of animal studies related to reproductive outcomes.

Mutagenicity

A West German study by Thiess et al. (1981) evaluated the rate of chromosome aberration in workers manufacturing ethylene oxide. Among the 43 males, aged 27-63 years, only those with long term exposure of more than 20 years were found to have a significant increase in chromosomal aberrations. Under normal plant operations, concentrations of ETO were below 5 ppm, and rose to as much as 1900 ppm for brief periods during occasional plant breakdowns. While findings indicate a mutagenic effect in long term exposure, the investigators pointed out that employees have been exposed to a number of other chemicals (e.g., chlorine, chlorinated hydrocarbons, phenol, etc). Therefore, the risk cannot be attributed to any one product.

A more recent investigation (Hansen et al.,1984) of hospital workers exposed to low levels of ethylene oxide reported no evidence of mutagenic effects. Lymphocyte analysis was performed on 14 exposed employees and matched controls to determine the distribution of sister chromatid exchange (SCE). In addition, Hansen and his coworkers obtained a history of the duration and extent of exposure, and information on possible confounders, such as alcohol, coffee, and cigarette consumption. Concentrations of ETO in all work areas were less than 5 ppm for an 8 hour time weighted average (TWA), and less than 50 ppm peak for 15 minute exposures. Overall, there was no indication that SCE levels in sterilizer workers were significantly different than those in controls. Smoking, however, was significantly associated with SCE induction (Lambert et al., 1982, cited by Hansen et al., 1984).

Male Exposure

No relevant data found.

Female Exposure

Pregnancy complications. A second investigation of hospital sterilization staff (Hemminki et al., 1982), revealed an increase in the rate of spontaneous abortion which was correlated with exposure to ethylene oxide. Women not exposed to the agent during pregnancy had a 7.8% rate of spontaneous abortion compared with a 16.1% rate for women exposed during pregnancy. Rates were adjusted for age, parity, smoking, alcohol and coffee consumption. In contrast, an increased rate of spontaneous abortion was not significant among women exposed to glutaraldehyde or formaldehyde, the other chemical sterilants examined by Hemminki and her associates. Concentrations of ETO in the Finnish hospitals have ranged from 0.1 to 0.5 ppm for the 8 hour TWA, with peak concentration of up to 250 ppm. Exposure levels were not measured in this study.

Comments

The limited number of reproductive studies on exposure to ethylene oxide make it difficult to assess its effects. The results of the two investigations of mutagenicity in lymphocytes of male workers are conflicting. Among females, an increase in spontaneous abortion appears to be associated with exposure to ETO. Evidence that ETO is mutagenic in vitro and in vivo, and OSHA's recent promulgation of a lower standard for this chemical, emphasizes the need to investigate further its possible reproductive effects.

Formaldehyde

Formaldehyde is colorless chemical with a pungent odor that irritates the exposed membranes of the eyes, noses and respirtory tract. Recently, it was found to be a nasal carcinogen in laboratory animals. Formaldehyde is ubiquitous in the human environment. It is a metabolic product of cigarette smoke and gasoline exhaust, and used as a food preserver and disinfectant (Federal Panel on Formaldehyde, 1982). Formaldehyde is an important chemical commodity with a worldwide volume of over 10 billion lbs/year (Gibson, 1983) . Workers in the medical, construction, textile, and wood and paper industries are susceptible to any of its potential reproductive effects (Federal Panel on Formaldehyde, 1982).

Animal Studies

There are limited studies on the reproductive toxicity of formaldehyde. In studies of mice no effects on pregnancy or dominant lethal effects have been observed. Similarly, a single study of female dogs showed no effects on pregnancy rate, litter size or malformations; however a decrease in body weight of the pups was observed. No relevant data is available on mutagenicity.

Male Exposure

No revelant data found.

Female Exposure

Menstrual disorders. Shumilina (1975), who conducted a study of 446 Russian workers exposed to urea formaldehyde resins in a fabric plant, found menstrual disorders in 47.5% of exposed fabric finishers and inspectors in contrast to 18.6% in the comparison group of 200 industrial sales women. Dysmenorrhea was the most common disorder reported. No test for statistical significance was performed, but the highest frequency of menstrual disorders occurred among the youngest women working, and among the fabric finishers where exposure was the greatest. Formaldehyde concentrations ranged from less than 0.05 ppm to 3.7 ppm, depending on the area of production.

Pregnancy complications. Shumilina (1975) indicated that anemia was the most frequent pregnancy complication. Although not analyzed for significance, this pregnancy complication was reported twice as often by the exposed group than the unexposed group. Hemoglobin was below 10g% in ten exposed women, as compared with four in the comparison group.

Pregnancy outcome: Spontaneous abortion. No significant difference in the frequency of spontaneous abortion was revealed among pregnant women sterilizing medical instruments with formaldehyde (8.4%) compared with nonpregnant women exposed to formaldehyde (8.3%) (Hemminki et al., 1982). Frequencies were based on total number of pregnancies, and rates were adjusted for age, parity, decade of pregnancy, smoking, alcohol and coffee consumption. The authors, who measured formaldehyde levels in sterilization units in Finnish hospitals as .03 - 3.5 ppm, suggest that exposure to formaldehyde may be minimal, particularly if gas chambers are used.

Neonatal health: Birth weight. In the Russian study (Shumilina 1975), children born to mothers exposed to formaldehyde had significantly lower birth weights than the controls' babies. Of the children born to mothers exposed to formaldehyde 27% weighed 2500-2990 grams. Only 11% of the controls' babies were found in this borderline low weight category.

Neonatal health: Congenital anomalies. Because formaldehyde is found commonly in the wood and insulation of homes in this country, its occurrence as an indoor air pollutant makes it a confounder in occupational studies. One descriptive study by Woodward and Zenz (1983) documents prenatal and neonatal illnesses in mobile homes in Wisconsin. The authors reported that, of 11 infants whose mothers lived for 7 or more months of their pregnancy in formaldehyde-contaminated homes, 2 had birth defects. This is about four times higher than the expected 5% data. Concentrations of formaldehyde in the homes of the infants were 0.54 and 2.76 ppm, sampled only once in the home prior to birth. Although these concentrations were among the highest taken in any homes, the investigators noted that average exposures during the pregnancies of the mothers may not be reflected in the samples.

Comments

There have been few studies on the female reproductive toxicity of formaldehyde, and of the ones conducted there is a lack of consistency in the findings. To date there have been no studies on male reproductive function. Of the two female investigations, one suggests an effect on menstrual function and pregnancy, while another indicates no significant increases in spontaneous abortion. Yet the widespread occurrence of formaldehyded in the workplace , as well as the potential for exposure to formaldehyde in the home to cause adverse reproductive effects, calls further investigation of its reproductive effects.

EPICHLOROHYDRIN

Because it is a highly reactive chemical, epichlorohydrin is used in the production of many products including epoxy resins, glycerol, paints, varnishes, shellacs, synthetic rubber, and pesticides.

Animal Studies

Epichlorohydrin has been shown to be mutagenic in bacteria and mammalian systems. In male rats, it causes infertility without recovery. In mice and rabbits, there is less evidence of reduced fertility. Possible histologic damage of the testes and epididymis have been suggested although not observed in male rats. Limited studies of pregnant female rats show no effects on litter size, resorption, or malformation rates. Epichlorohydrin is carcinogenic in mice, but no transplacental carcinogenesis has been observed (Barlow and Sullivan, 1982).

Mutagenicity

Evidence suggests that epichlorohydrin may be mutagenic in humans. Kucerova (1977), in a study of the lymphocytes of 35 workers, found an increase in the number of chromosomal aberrations after 1 year of exposure to epichlorohydrin compared with the number of aberrations in each worker before exposure. Sram and coworkers (1976) also found chromosomal abnormalities in human peripheral lymphoctyes after in vitro exposure to epichlorohydrin (cited in NIOSH, 1978).

Male Exposure

Semen quality. Milby et al.(1981) studied testicular function in 2 cohorts of workers at 2 plants where epichlorohydrin was produced. Semen of 138 of a total of 216 eligible workers was compared with a 90 member control group. In both plants, no significant differences were found between sperm count distributions in exposed workers and the control group. Further, no relationship was found between sperm count and either duration or intensity of exposure.

Infertility. A study by Venable and coworkers (1980), examined the fertility status of 64 men employed in the glycerine department of a Texas industrial chemical plant. Epichlorohydrin was one of 3 three-carbon compounds produced. The other two were allyl chloride and 1,3-dichloropropene. All of these are structurally related to DBCP, a pesticide known to cause sterility in male workers. Employees were divided into three chemical subgroups on the basis of their work areas: 1) epichlorohydrin and allyl chloride; 2) allyl chloride and 1,3-dichloropropene; 3) epichlorohydrin, allyl chloride and 1,3-dichloropropene. Employees were also classified by "strength of exposure" (a subjective measure), and duration of employment. No associations were shown between lowered fertility and exposure to epichlorohydrin, allyl chloride or 1,3-dichloropropene when comparisons were made between the 64 exposed and the 63 unexposed employees. Further, there were no differences between the three groups in fertility measures. Fertility was measured by such variables as sperm count, percent viable sperm, and sperm motility among others. Exposure to the chemicals was estimated at 1 ppm determined as a time weighted average.

Female Exposure

No relevant data found.

Comments

The evidence from human studies of epichlorohydrin has shown no effects of exposure upon male fertility as demonstrated by a number of measures of semen quality. Studies have shown that epichlorohydrin may be mutagenic causing human somatic cell chromosomal changes both in vitro and in vivo.

Only effects upon the male reproductive system have been studied to date. Other outcomes such as pregnancy outcome of female partner of the male worker have not been studied. Female reproductive effects from epichlorohydrin also have not been studied.

HORMONES

Synthetic hormones have a variety of uses ranging from supplements in animal feeds to human therapeutic agents such as oral contraceptives and cancer therapeutic agents. Occupational exposure to synthetic hormones mainly occurs during production in pharmaceutical plants. Exposure is usually to synthetic estrogens (ethinyl estradiol, diethylstilbestrol) or progestogens.

Male Exposure

Semen quality. Mills et al. (1984) found a slightly but not significantly lowered sperm count (59 v 65 million sperm per ml) and a slightly lowered ejaculate volume (3.08 v 3.82 ml) among 22 workers exposed to synthetic estrogens and progestogens compared to 42 controls.

Potency and libido. In the same study, Mills and coworkers (1984) found a nonsignificant decrease in libido among hormone-exposed workers compared to nonexposed workers (32% v 17%). Harrington et al. (1978) found that 3 of 4 employees at one job site had experienced impotence. Exposure levels in this study for 6-7 hour personal air samples showed nondetectable to 8.61 ug/m3 for mestranol and nondetectable to 43.2 ug/m3 for norethindrone.

Physiologic changes. Hormonal and body changes were reported secondary to hormone exposure in the workplace. Harrington et al. (1978) studied mestranol and norethindrone exposure and found evidence of gynecomastia in 4 of 4 employees at one job site and galactorrhea in 1 employee. Although not significant statistically, Harrington et al. (1978) found that 20% of 25 male hormone-exposed workers had clinical gynecomastia or a history of it. Mills and colleagues (1984) studied 22 hormone-exposed men and found significantly more than the control group had experienced breast swelling or tenderness (36%), had breast lumps or nodules (87%), and had lower total estrogen levels (23.8 pg/ml v 37.5 pg/ml). No males showed detectable evidence of ethinyl estradiol, however 50% of exposed males had measurable levels of norethindrone (statistical significance not given).

Female Exposure

Menstrual disorders. Harrington et al. (1978) found among 24 female employees exposed to mestranol and norethindrone, 12 (50%) experienced intermenstrual bleeding, compared with 17% of the 60 controls. This reflected a relative risk of 4.26 for factory workers compared to controls matched on age, sex, and socio-economic status. Mills et al. (1984) found menstrual changes in all 6 women studied with 83% complaining of irregular cycles compared with 4/12 (33%) of controls (not statistically significant).

Physiologic changes. In hormone-exposed females, Mills and coworkers (1984) found that mean total serum estrogen levels were significantly lower (28.2 pg/ml) than in unexposed females (76.6 pg/ml). No females had detectable evidence of synthetic hormones in their blood.

Comments

Synthetic hormones have been shown to have reproductive system effects on both males and females. In men, breast swelling and tenderness as well as breast lumps or nodules were seen. In women, menstrual problems, especially abnormal bleeding, dominated. In both males and females, serum estrogen levels were depressed.

There have been very few studies of the reproductive effects of exposure to synthetic hormones on workers. Studies that do exist are notable for their efforts to measure workplace exposure levels of the hormones, for their use of measures of exogenous hormone levels as exposure indicators, and for their focus on exposure to both males and females.

Certain methodologic problems complicate studies of this type such as difficulty in measuring the clinical effects of exposure, some of which are very subjective (e.g. complaints of loss of libido) and others which are difficult to measure (e.g. gynecomastia), and problems in identifying the most appropriate indicators of exposure and outcome.

METALS

In this section we discuss the reproductive effects of metals which have been investigated in humans. These include in alphabetical order: antimony, arsenic, boron, cadmium, lead, and methylmercury. Other metals such as chromium, nickel, selenium, lithium, and copper have been found to have reproductive effects in animals but have not been examined in humans.

Antimony

A Russian study (Belyayeva, 1967) found that women working in an antimony metallurgy plant had a higher incidence of "reproductive system disorders", premature births, and spontaneous abortions. Their infants did not gain weight as rapidly as infants of controls.

Arsenic

Mutagenicity

Increased frequency of chromosomal aberrations have been observed in the lymphocytes of wine growers exposed to arsenic pesticides (cited by Nordenson et al., 1978) and in patients with psoriasis treated with arsenic (Burgdorf et al., 1977). Skin carcinoma has been observed in the latter group years following treatment (Braun, 1958). Nordenson et al. (1978) found an increased frequency of chromosomal aberrations among arsenic-exposed workers at the Rönnskär smelter in northern Sweden compared to healthy males from a nearby city. The groups with higher exposure had a greater frequency of aberrations including gaps and chromatid aberrations. There seemed to be an interaction between smoking and arsenic exposure but smoking was not controlled for in the analyses.

Male Exposure

Pregnancy outcome of female partner. Hemminki and Niemi (1982) examined the rates of spontaneous abortion in a community where a metallurgic industry was located. The industry produced mostly zinc and cobalt and emitted into the environment sulfur dioxide, hydrogen sulfide and arsenic and to a lesser extent, cadmium and mercury. Twenty-five percent of the men were employed there; most of the women were employed in the textile industry. The wives of workers in the metallurgic industry had slightly higher frequency of spontaneous abortions (11.5%) than wives of all industrial workers (9.3%)(see Industrial Studies for detailed description).

Female Exposure

Although animal studies suggest that inorganic arsenic readily crosses the placenta (Morris et al., 1938), few studies have reported adverse effects of arsenic on the human fetus following maternal exposure.

Pregnancy outcome: Spontaneous abortion. Hemminki and coworkers conducted a series of studies on workers in the metallurgy industry in Finland. These workers are exposed mainly to arsenic as well as sulfur, zinc, cobalt, and copper. In a study based on membership in the Metal Workers Union between 1973-1976, Hemminki et al. (1980) found that the ratio of spontaneous abortions was significantly higher among the 35,000 metal workers (13.8%) than in the general population of Finnish women (10.3%). The frequency of spontaneous abortions was highest for women employed in the electronics industry (16.5%) and in radio and television production (20.9%). The authors suggested that possible occupational hazards include fumes from soldering. Parity was not controlled for in the analyses.

In an update of this study which included membership up to 1979, Hemminki and coworkers (1983) reported no difference in the age standardized-ratio (number of spontanous abortions/births) of spontaneous abortions for pregnancies during the women's membership in the Union (7.8%) and for pregnancies before or after Union membership (7.1%). Spontaneous abortions were significantly more frequent for melters (21%) than for other Union members but the numbers were small (N=7).

Neonatal mortality. Lugo et al. (1979) reported a case of a woman 30 weeks pregnant who ingested 30 ml of arsenic trioxide. Three days later she delivered a livebirth weighing 1100 gms. who died 11 hours later. Autopsy revealed hyaline membrane disease and substantial levels of arsenic in the liver, kidneys and brain. Although this was not a occupational exposure, this study demonstrated that arsenic readily crosses the placental barrier.

Boron

Animal Studies

Animal studies on boron have focused on male testicular effects. In both rats and dogs testicular atrophy and decreased testicular weight have been shown. In addition, one study on rats revealed decrease in sperm count and motility. The few studies on female rats suggest decreased ovarian weight and litter sizes at high doses.

Male Exposure

Semen quality. Soviet studies reported oligospermia and decreased libido in men living in communities where boron concentration was high in the well-water (Khachatrian and Nazarenko, 1973, cited by Lee, 1983; Krasovskii et al., 1976) and in men working in factories where boric acid was produced (Tarasenko et al., 1972, cited by Lee, 1983).

Female Exposure

No relevant data found.

Cadmium

Mutagenicity

Chromosomal studies have revealed inconsistent results concerning the mutagenicity of cadmium. No significant chromosomal aberrations were found when cadmium chloride was added to human leukocyte or fibroblast cultures, or in investigations of the blood lymphocytes of men working in the manufacture of cadmium pigments (O'Riordan et al., 1978), men working in an alkaline battery factory, and in female patients with Itai-itai disease, a disease endemic to a cadmium-contaminated area in Japan (Bui et al., 1975). However, Shiraishi and coworkers (Shiraishi et al.,1972; Shiraishi and Yosida, 1972; Shiraishi, 1975) have reported chromosomal breakages and rearrangements in patients with Itai-itai disease, and in cultured lymphocytes treated with cadmium sulfide. Bauchinger et al. (1976) observed similar chromosomal damage in the blood lymphocytes of zinc smelting plant workers who had increased blood levels of cadmium as well as lead. Unlike Deknudt et al. (1973) who suggested that lead intoxication was responsible for the chromosomal aberrations, Bauchinger concluded that the aberrrations were either due to cadmium exposure or the synergistic effect of both exposures.

Male Exposure

Semen quality. Cadmium is an excellent spermicide in that in the presence of cadmium, motility of human spermatozoa declined to about 33% of the control values after 1 hour and 0% after 3 hours (Holland and White, 1980).

Female Exposure

Placental transfer. The placenta provides a substantial barrier to the passage of cadmium to the fetus (Roels et al., 1978). Cadmium levels are highest in the placenta and are typically about 20% to 50% lower in newborn blood than maternal blood (Baglan et al., 1974; Lauwerys et al., 1978). One Japanese study of women living in a large city found cadmium levels unexpectedly higher in cord blood than maternal blood but the levels of cadmium were very low in the placenta, and in maternal and fetal blood (Tsuchiya et al., 1984). Kuhnert et al. (1982) found that women who smoked have significantly higher levels of cadmium in their blood than nonsmokers, however, cadmium levels in the blood of their fetus' was only slightly higher. Although the reduced transfer of cadmium to the fetus and its accumulation in the placenta may seem safer for the fetus, cadmium could alter the placenta's protective function (as seen in animal studies) and thereby, indirectly lead to embryotoxicity (Parizek, 1965; Roels et al., 1978).

Pregnancy outcome: Stillbirths. The ribs and vertebrae of 42 stillborn infants contained on average ten times the amount of cadmium than the bones of a much older group of adult accident victims (Bryce-Smith, et al., 1977).

Neonatal health: Birthweight A Soviet investigation did not find abnormalities in the menstrual cycle, pregnancy, or delivery of 106 women employed in the manufacture of alkali storage batteries. However, the investigators did find a significant decrease in the birthweight of their infants (Tsvetkova, 1970). These women were exposed to concentrations of cadmium between 0.03 and 35 mg/m3.

Lead

Lead exposure occurs not only in the workplace but in the ambient environment. Pregnant women and children can be exposed to lead by contaminated work clothing brought into the home (Baker et al., 1977), by proximity to lead smelter plants or battery factories (Elwood et al., 1977) or to highways (Annest et al., 1983), by drinking water contaminated by lead plumbing (Moore et al., 1982), or by inhalation or ingestion of lead-based paints. National estimates of blood lead levels reveal that 18.6% of black inner-city children have lead levels considered to be in the toxic range (Mahaffey et al., 1982) and that lead levels in the United States seem to vary directly with the allowable lead content in gasoline (Annest et al., 1983).

Mutagenicity

Cytogenic studies have demonstrated chromosomal aberrations in workers exposed to lead. Increased rates of chromosomal gaps and breaks, and chromosomal abberrations have been reported in the cultured lymphocytes of workers exposed to lead and arsenic while employed in a smelter plant in Northern Sweden. The number of chromosomal aberrations was dose-related to blood lead levels of the workers; 73% of the workers had an increased frequency of aberrations. The authors concluded that an increased risk of chromosomal damage can be found at lead levels of 25 mcg/dl (Nordenson et al., 1978).

Increased frequency of abnormal cell divisions (metaphases) was also noted in the cultured lymphocytes of women working in a storage battery plant (average lead levels of 42 mcg/dl) when compared to controls with average lead levels of 28 mcg/dl (Forni et al., 1978). Serial chromosomal studies of these workers found that the rate of chromosomal aberrations almost doubled after working with lead for the first month, increased for the next 2 months and then plateaued with a slight decrease after 7 months of exposure. This pattern almost paralleled their increase in blood lead levels (Forni et al., 1976). Schwanitz et al, (1970) compared a group of healthy blood donors with workers in a lead oxide factory who had average lead levels of 74.7 mcg/dl. They observed significantly more abnormal mitoses with secondary chromosomal aberrations in the blood of the workers. Other studies which have found a positive association of lead and chromosomal abnormalities include studies on blast furnace workers (Schwanitz et al., 1975; cited by Thomas and Brogan, 1983), battery melters (Deknudt et al., 1977; cited by Thomas and Brogan, 1983), and ceramic, lead, and battery workers (Sarto et al., 1978; cited by Thomas and Brogan, 1983).

In a number of studies it is difficult to conclude whether lead exposure is associated with chromosomal aberrations. These studies are difficult to interpret because the worker has had multiple exposures. In a study of workers in the zinc industry who were exposed to cadmium and lead, Deknudt et al. (1973) suggested that lead was responsible for the chromosomal aberrations observed, but Bauchinger et al. (1976) who also reported increased chromosomal gaps in the lymphocytes of workers in the zinc industry concluded that the aberrations were induced either by cadmium alone or by both metals together, but not by lead (see Cadmium).

A few studies which have not found chromosomal aberrations in workers exposed to lead have employed control groups with fairly high lead levelsor with greater than the expected number of chromosomal abnormalities. O'Riordan and Evans (1974) found no increase in the number of chromosomal aberrations in workers exposed to lead oxide as burners in a shipbreaking yard (lead levels greater than 40mcg/dl); however, both the burners and the "control" group had increased chromatid aberrations compared to the general population.

Other studies which have failed to find an association between lead and chromosomal abnormalities include studies of policemen (Bauchinger et al., 1972; cited by Thomas and Brogan, 1983), lead workers (Schmid et al., 1972; cited by Thomas and Brogan, 1983), and of volunteers who ingested lead (Bulsma and DeFrance, 1976; cited by Thomas and Brogan, 1983).

Male Exposures

Semen quality. Since the days of the Roman empire, lead has been thought to be a cause of infertility in men (Gilfillan, 1965). However, only recently have investigators examined the fertility and semen quality of men exposed to lead (Lancranjan et al., 1975; Braunstein et al., 1978; Cullen et al., 1983). Lancranjan et al. (1975) reported a relatively high frequency of decreased libido and sexual dysfunction in workers in a storage battery plant compared to men working in a less polluted environment. The investigators carried out semen analyses on 89 workers and found a dose-response relationship between blood lead levels and decreasing sperm counts and sperm motility, and an increasing proportion of abnormal sperm. For the workers with relatively low-level exposure (average blood lead level=41 mcg/dl), only count and motility were different from controls; for the lead poisoned workers (average blood lead level=74.5 mcg/dl), count, motility, and proportion of normal forms was different from controls. As many as 50% of the lead-poisoned workers were considered infertile. No significant changes were noted in androgen secretions (ketosteroids) and in urinary gonadotropins, and therefore, the authors concluded that lead had a direct toxic effect on the gonads.

Braunstein et al.(1978) found that 5 out of 10 lead-exposed men who presented with a complaint of impotence had abnormally low sperm counts. Testicular biopsies of two azoospermic men revealed fibrosis and depressed spermatogenesis. Cullen et al. (1983) also found complete absence of sperm or oligospermia in 5 out of 14 workers. These workers had average blood lead levels of 65.4 mcg/dl (range between 40 and 83 mcg/dl) at the time of analysis and had had maximum lead levels averaging 85.6 mcg/dl. All 3 with low sperm counts had an increased proportion of abnormal forms. Gonadotropin levels were normal in 11 out of 13 of the workers, and prolactin and testosterone levels were normal in all but one. Normal prolactin, FSH, LH, and testerone levels in lead-exposed workers have been reported in another unpublished study (Molini et al., 1981; cited by Wildt et al., 1983).

Wildt et al.(1983) found no difference in sperm count, motility, and abnormal forms in workers whose lead levels averaged 45 mcg/dl compared to workers whose average lead level equalled 22 mcg/dl. A large percentage of the lower lead exposed group had symptoms of prostatitis, an infection which might reduce the motility of the sperm. The authors did find a decrease in sperm chromatin stability and prostate secretions in the higher lead group.

Pregnancy outcome of female partner. Investigators at the turn of the century observed that wives of lead workers showed a high abortion and stillbirth rate (Rudeaux, 1905; Rom, 1976). A more recent study has not corroborated these early findings. Workers at a copper smelter plant are exposed during the smelting process to lead as a contaminant of the copper ore, as well as a variety of other metals (arsenic, mercury, cadmium). Beckman and Nordström (1982) examined the pregnancies of 519 wives of these workers and observed that pregnancies after the husband's employment at the smelter were not more likely to end in spontaneous abortion or in infants with congenital malformations than pregnancies before the husband's employment. Pregnancies after employment were more likely to result in fetal death even after parental age and gravidity were controlled.

Female Exposure

For over a century, authors have suggested that lead exposure may be related to amenorrhea and other menstrual disorders, infertility, spontaneous abortion, stillbirth, and neonatal deaths (Paul, 1860; Oliver, 1911; Legge and Goadby, 1912; see Rom, 1976, 1980, and Gerber et al., 1980 for review). In fact, lead was used to induce abortion (Hall, 1905;Taussig, 1936; cited by Gerber et al., 1980). Women exposed to lead in pottery glazing had been reported to have as high as 60% of their pregnancies end in miscarriage (estimates range around 10-15% in the U.S. at the present time)(Pindborg, 1945; cited by Rom, 1976), and as high as 71% of their livebirths having either macrocephaly or convulsions (Rennert, 1881; Chyzzer, 1908; cited by Rom, 1976). Women exposed to lead in the printing industry were at least 3 times more likely to abort than expected, and they were twice as likely to have children who died (Torelli, 1930; cited by Rom, 1976). Although exposure during these early times was probably higher than today (Bridbord, 1978), lead exposure of women still seems to pose a risk to reproduction.

Female Exposure

Placenta transfer. Lead readily crosses the placental barrier with relatively little lead concentrating in the placenta (Roels et al.,1978). Barlthrop (1969) found that placental transfer of lead began in the 12th week gestation and lead concentrations in the fetus increased throughout gestation. Lead concentrated mostly in the bone of the fetus but also in the blood, brain, heart, and kidney (Carpenter, 1974).

Blood leads levels of the mother and neonate usually correlate (Gershanik et al., 1974; Zetterlund et al. 1977; Lauwerys et al.1978; Tsuchiya et al., 1984) with the mother's level in most studies reported to be only slightly higher (Harris and Holley, 1972; Gershanik et al.,1974; Osborne et al., 1976; Zetterlund et al., 1977; Rabonowitz and Needleman, 1982; Tsuchiya et al, 1984). However, one study which used measures of zinc protoporphyrin, a more accurate measure of long-term exposure than the standard blood lead level, found higher lead levels in fetal cord blood than in maternal blood (Angell and Lavery, 1982). Population studies have found average lead levels in fetal cord blood to range from 6.6 mcg/dl to 24.2 mcg/dl (Scanlon, 1972; Rajegowda et al., 1972; Harris and Holley, 1972; Gershanik et al., 1974; Baglan et al., 1974; Osborne et al., 1972; Zetterlund et al., 1977; Elwood et al., 1978; Lauwerys et al., 1978; Rabinowitz and Needleman, 1982; Tsuchiya et al., 1984). Lead levels tend to be higher in fetuses of mothers who work with lead (33 mcg/dl in an infant of a storage battery worker, Ryu et al.1978; M=17 mcg/dl, Alexander and Deldes,1981), who drank water drawn from lead piping (Elwood et al.,1978), and who live in polluted urban areas (Osbourne et al., 1976; Zetterlund et al.,1977). Since the early 1970's, lead levels in the cord blood of infants have been decreasing annually by as much as 7 to 11% in certain urban areas (Rabinowitz and Needleman et al., 1982).

Seasonal variations of lead levels are inconsistent: Rabinowitz and Needleman (1982) found higher lead levels in the cord blood of infants born in the summer, Dawson et al.(1968) and Baglan et al.(1974) found higher concentrations in infants born in the late autumn or winter, Wibberley et al. (1977) noticed the lowest levels in May, and Zetterlund et al.(1977) found no seasonal variation.

Breast milk. Lead has been found in breast milk at concentrations ranging between 6 and 58 mcg/l (ppb) with an average concentration of 26 mcg/l (Dillon et al., 1974). Earlier studies have shown levels as high as 100 mcg/l in the United States (Kehoe, 1933), and 1500 mcg/l in Belgium (Noirfalise et al., 1967; cited by Dillon et al., 1974). A women exposed to lead for 3 months during her pregnancy in the course of manufacturing storage batteries, had blood lead concentration of 33 mcg/dl at delivery, and breast milk lead concentrations ranging between 19 and 63 mcg/l during the first few weeks of lactation. Although she had terminated employment, lead level in her milk increased in the second month of lactation to 36 to 62 mcg/l, and then gradually decreased to 4 to 14 mcg/l in the next 4 months. Lead ranged between 15 and 65 mcg/l in the breast milk of 9 controls not exposed to lead (Ryu et al., 1978). Wolff (1983) noted that although this women's blood level was 3 times that of controls, the lead concentration in her breast milk was almost the same. It is important to note that the lead content in an infant's diet including formula or cow's milk has less than 1 ppb (Johnson et al., 1981; cited by Wolff, 1983).

Pregnancy complications. Fahim et al. (1976) compared the pregnancies of 253 women who lived for at least 10 years near lead mining areas in Missouri with the pregnancies of 249 women who lived at least 85 miles away. They observed a 42 times increased risk for fullterm pregnancies to have premature rupture of the membranes (12 hours before delivery) and a 4.3 times increased risk for premature deliveries (before 37 weeks). There were no significant differences in lead concentrations (mother or infant) of term pregnancies between the two regions. Lead levels were significantly elevated in maternal and fetal blood in deliveries with premature membrane rupture and preterm pregnancies compared to blood lead levels in term deliveries. The elevated lead levels were on average greater than 25 mcg/dl for maternal blood (average for term delivery was less than 14 mcg/dl) and greater than 9.6 mcg/dl for fetal blood (average for term was less than 5 mcg/dl).

Angell and Lavery (1982) could not duplicate Fahim et al.'s findings in a population of 635 women who had somewhat lower lead levels (average = 9.8 mcg/dl). No differences in lead levels were observed in maternal or fetal blood in pregnancies with premature rupture, preterm delivery, preeclampsia, or meconium staining than for term deliveries without pregnancy complications. However, two women with lead levels greater than 25 mcg/dl both had pregnancy complications (preterm and meconium).

Pregnancy outcome: Spontaneous abortion. In an early Japanese study, Nogaki (1958) found a two-fold increase in miscarriage rate in women working with lead compared to their miscarriage rate during their preemployment period. Their blood lead levels were extremely high ranging from 110 mcg/dl to 317 mcg/dl.

Nordström and coworkers have conducted a series of studies investigating the reproductive hazards associated with working at or living near a smelter in Northern Sweden. The smelter manufactures copper, lead, and a number of metallurgic and chemical products. The smelter emits lead as well as arsenic and sulphur dioxide. Upon investigating all pregnancies of all women employed at the smelter between 1930 and 1959, the authors observed the highest frequency of spontaneous abortion in women employed at the smelter during pregnancy and who also lived close by (28%)(Nordström et al., 1978; 1979). Women involved directly with the smelting process had higher rates of miscarriage than other employees. Women were slightly more likely to abort if both they and their partner worked at the smelter. In a community study examining all pregnancies since 1930 (N=4544), Nordström and coworkers found that the highest rate of miscarriage occurred among women who lived closest to the smelter (11%) and the lowest rate among those who lived furthest away (7.6%). However, all estimates of spontaneous abortion were crude rates with neither parity, maternal age, nor any other confounders controlled.

Pregnancy outcome: Stillbirths. Three groups of investigators have examined lead levels in tissue of stillbirths. Two groups found over three times the lead in ribs of stillbirths (Bryce-Smith et al., 1977: average=5.7 mcg/g; Khera et al., 1980: average= 2 mcg/g) than in ribs of infants who died from causes such as cot death (Bryce-Smith et al: range = 0.2 to 0.6 mcg/g; Khera et al.: average= 0.7 mcg/g). Placental lead levels in one study reached 1.5 mcg/g in only 7% of normal births but in 61% of the stillbirths (Wibberley et al., 1977). A third study (Barry, 1981) found significantly less lead in the ribs of stillbirths than in those of neonatal livebirths. These livebirths seemed to have died from causes (e.g. prematurity, preeclampsia, intrauterine asphyxiation, congenital malformations) different from those in the previous two studies. Studies which compare tissue from stillbirths with tissue from neonates who die of illness or malformation should be interpreted with caution since placental lead levels have been found to be higher, in general, in infants who die during the neonatal period (Wibberley et al., 1977).

Wilson (1966) reported a stillbirth with increased lead levels in the kidneys and whose mother had increased levels.

Neonatal health: Birthweight. Wibberley et al. (1977) found no association of placental lead and birthweight in normal livebirths sampled from a maternity hospital. However, Nordström et al. (1978, 1979) found that birthweight was significantly lower in infants of women employed at a copper and lead smelter at the time of their pregnancy than for infants born in a nearby city. The difference in birthweight was decreased mainly for later pregnancies and for women living near the smelter. (Birthweight normally increases with parity.) Women directly involved with the smelting process had significantly lighter babies than other employees. However, smoking history, maternal age, parity and other confounders were not controlled. Women not employed in the smelter but who lived nearby were also more likely to have lighter babies especially in their later pregnancies than women who lived further away (Nordström et al., 1978). The authors suggested that the mother's cumulative exposure to lead might account for this unexpected parity effect.

Neonatal health: Congenital malformations. A study based on a small number of malformed infants (N=9) found no elevation of lead levels in their placental tissue. Lead levels were increased in tissue of malformed infants who also showed fetal distress (N=10)(Khera et al., 1980).

In another study based on the Rönnskär smelter in northern Sweden, Nordström and coworkers (1979) found that women employed during their pregnancy were about twice as likely to have an infant with malformations (5.8%) than women who worked at the smelter but not during their pregnancy (2.2%), or than other women living in the region (2.9%). Women working at the smelter were four times more likely than women living in the region to have infants with multiple malformations. These are all crude estimates; no confounders were controlled for in the analysis. Although the number of pregnancies were too small to statistically analyze specific malformations, the authors noted that 3 women had infants with cleft lip or palate (1.2%) which was about 10 times higher than expected based on regional statistics.

Needleman and coworkers (1984) examined the relationship of cord blood lead levels and congenital malformations in an epidemiological study of all liveborns delivered during a one year period at Boston Hospital for Women (5183 women, 84% interviewed). They found that lead levels were dose-related to the incidence of minor malformations in general including such malformations as hemangiomas, hydrocele, skin anomalies, and undescended testicles but were not significantly related to any single minor malformation. Potential confounders such as maternal age, birth weight, gestational age, and race were included in the model. Infants with cord lead levels of 6.3 mcg/dl, the average lead level for this population, were almost twice as likely to have a minor malformation at birth.

Neurodevelopment. In utero lead posioning. There exist a number of case reports of in utero leads poisonings and subsequent neurodevelopment of the infant.

An infant was exposed between the 5th and 8th months of gestation when his family burned battery casings for fuel (Angle and McIntire, 1964). His mother had been given a course of a chelating agent, Ca EDTA, during the 8th month of pregnancy. The infant had normal lead levels at delivery and seemingly no ill effects from the Ca EDTA. He showed normal development at age 4.

An infant was exposed to lead in utero when his mother worked in a storage battery plant. Cord lead levels reached 33 mcg/dl. The infant had a normal physical and neurological exam at birth, and normal motor and social development at age 9 months (Ryu et al., 1978).

A 10 week old infant whose mother drank "moonshine" (untaxed whiskey) had a peak 24 hr urine lead level of 620 mcg/l (Palmisano et al., 1969). The infant demonstrated pre- and postnatal growth retardation, hyperreactive reflexes, increased muscle tone, spastic stepping movements, and tremors in the arms and legs. These symptoms may have resulted from in utero exposure to alcohol as well as to lead.

Singh et al. (1978) described an infant with blood lead levels of 50 mcg/dl at delivery who was treated with Ca EDTA at 3 weeks of age. The infant was exposed to lead in utero when both parents were engaged in torching and scraping old paint off their house. Although at birth and 10 months the infant's physical and neurological exam appeared normal, at 13 months her cognitive skills were at the 8-12th month level, her receptive language skills were at the 8-9th month level, and her expressive skills lagged even further behind at the 6-7th month level.

Neurodevelopment: Subclinical effects. Many studies have investigated the association of lead levels and neuropsychological performance in school-age children (see Rutter, 1980, for review). Even relatively low levels of lead exposure have been associated with lower IQ's (e.g., Landrigan et al., 1975), poorer academic skills (e.g., Pihl and Parkes, 1977), increased motor activity (e.g., Needleman et al., 1979), and hyperactivity (e.g., Gittelman and Eskenazi, 1983). The scientific literature has had a profound influence on lowering the lead levels allowed by law in the environment and in gasoline.

In spite of the vast literature on lead and school-age children, there is a paucity of published information on in utero exposure and subsequent neuropsychological development. Presently, at least six large scale prospective studies are underway (Chisolm and Thomas, 1983)

In the United States, Needleman and associates (1983) have gathered the cord blood levels of almost 10,000 livebirths delivered over a two year period at one hospital. In a preliminary report, these authors selected 76 infants with cord lead levels greater than 12.5 mcg/dl, 88 with levels between 6 and 7 mcg/dl, and 85 infants with less than 3 mcg/dl. They evaluated these infants at 12 months on the Bayley Scales of Infant Development and on scales of temperament and social adjustment. Infants with high lead levels tended to be less predictable and to be more impaired in motor development.

In Scotland, Beattie et al. (1975) conducted a retrospective study of 77 mentally retarded children between the ages of 2 and 6 and found higher lead levels in homes where their mothers lived during pregnancy than in homes of mothers of nonretarded infants who were matched for social class. In a subsequent study on a subsample of these children, Moore and coworkers (1977) retrospectively measured these children's blood lead concentrations within the first two weeks of life by an atomic absorption technique employing the cards used to evaluate phenylketonuria. The mentally retarded children had had higher concentrations of lead.

Currently, the Scottish group is engaged in a long-term prospective study of 151 mothers and their infants. The participants are drawn from the 885 who originally took part in the Duplicate Diet Study of Great Britain. Glasgow was chosen because the lead content of drinking water has been a source of overexposure. As part of the Duplicate Diet Study, each woman had blood lead and domestic water lead concentrations measured. For a subsample of these women, samples of maternal blood, cord blood, and infant blood (at10 weeks of age) was obtained. Analysis was also made of lead intake from food and water. (The Duplicate Diet Study revealed that children received the greatest intake of lead from their food.) Moore and coworkers have divided the 151 subjects into 3 exposure groups: women with blood lead greater than 30 mcg/dl, those with 15-25 mcg/dl, and those with less than 10 mcg/dl. This study probably includes women and infants with somewhat higher lead exposure than in the prospective study conducted by Needleman and associates. The Scottish group plans to follow these children up to age 5. Children will be evaluated on a variety of tests of IQ, hyperactivity scales, and language skills over the five year period (Moore et al., 1982).

The other four prospective studies will use many of the same neurodevelopmental measures as the Boston and Scottish groups. The sites of investigation include (Chisolm and Thomas, 1983):

1. Cincinnati: a prospective study based on a predominantly black inner city population with most of the exposure occurring postnatally;

2. North Carolina: followup of children 12 to 60 months of age whose mothers worked in a battery factory;

3. Port Pirie, Australia: a prospective study ofchildren living near a smelter. The lead levels are anticipated as high as 50 mcg/dl;

4. Sydney, Australia: a prospective study based on a predominantly white urban population. Lead levels are expected to lie between 10-15 mcg/dl, with few values exceeding 30 mcg/dl.

Methylmercury

Mercury and one of its organic compounds, methymercury, readily cross the placenta in humans and animals. Although both inorganic and organic mercury have been shown to have adverse reproductive effects in animals (see Animal tables), only the ill-effects of methylmercury are well-known for human populations.

Occupational exposures to methylmercury have been reported in workers who manufactured the fungicide (Hunter et al., 1940) and in fishermen in Minamata Bay who ate contaminated fish (Tokuomi et al., 1961). However, most of the exposure to methylmercury has not been in the workplace but in the home, that is, through the ingestion of contaminated fish or seed grain. Accumulation of mercury occurs in predatory fish in the ocean, and fish which come from inland lakes that are contaminated from the effluents of chloralkali plants and paper mills

(Weiss and Doherty, 1975). Another source of mercury poisoning is by the ingestion of seed grain coated with mercuric fungicide. Although methylmercury is no longer used as a fungicide in the U.S., other mercuric compounds are still in use. Perhaps the largest cause of mercury contamination in the air is as a by-product from the burning of coal and other fossil fuels (Joselow et al., 1972).

Most of the reported exposures to methylmercury have occurred during 2 major environmental disasters: one in Minamata Bay around 1953 and the other in Iraq in 1971(see Elhassani, 1982 for review). The Minamata Bay disaster resulted after mercury was discharged into the bay as wastes from a plant producing acetylaldehyde and vinyl chloride. Microorganisms in the bay methylated the mercury. Fish ate the methylated mercury and the inhabitants around the bay ate the contaminated fish. More than 800 adults and children, and 40 fetuses were poisoned. A similar accident occurred between 1953-1960 in the Agano River in Niigata, Japan. In Niigata, 46 cases were identified but only 1 fetal poisoning (Takizawa, 1970; cited by Koos and Longo, 1976).

In Iraq, the outbreak of methylmercury poisoning resulted from accidental ingestion of seed grain treated with a methylmercury fungicide (Bakir et al., 1973). More than 6000 persons were admitted to hospitals and at least 80 cases of in utero poisoning were identified (Bakir et al., 1973). Mothers showed symptoms of poisoning at blood mercury levels above 300 ppb; infants showed symptoms of poisoning at blood mercury levels above 564 ppb(ng/ml) and were severely affected with mercury levels above 3000 ppb. or with maternal hair concentration above 371 mcg/g (Amin-Zaki et al., 1979). The most severe effects occurred, e.g. cerebral palsy, if the infant was exposed during the third trimester in utero. Pitkin et al. (1975/6) reported fetal blood mercury levels in an unexposed population averaging at 1.2 ng/gm; methylmercury levels in Iran were measured at levels between 700 and 1000 times higher (Bakir et al., 1973).

Unlike the poisoning at Minamata which was prolonged (for almost a decade until it was identified), the exposure in Iraq was to higher doses over a period of only 3 months. Whereas Iraqi infants were examined 6 days to 7 months after birth, Japanese infants were first examined between 1 and 7 years. Iraqi women continued to expose their infants by breastfeeding; Japanese women did not breastfeed. Differences in the intensity and duration of exposure, and in the age of the subjects at the time of examination may account for slight discrepancies in the effects of these two accidents.

Other methylmercury accidents involving fewer people have occurred in Sweden (Engleson and Herner, 1952), Pakistan (Haq, 1963), Guatemala (Ordonez et al., 1966), Soviet Union (Bakulina et al., 1968), the United States (Snyder, 1971; Pierce et al., 1972) and more recently, in Canada (McKeown-Eyssen et al., 1983). In Pakistan and Guatemala, no fetal cases were reported.

Engleson and Herner (1952), in Sweden, were the first to report a case of fetal exposure to methylmercury. In utero exposure occurred following the mother's ingestion of contaminated flour. The infant had a mercury urine level less than .003 mcg/ml and the mother had no symptoms of poisoning (above .1 mcg/ml is considered excessive exposure; see Joselow et al., 1972). In the Soviet Union, Bakulina (1968) reported 10 cases of infants exposed prenatally to ethylmercury when their mothers ingested contaminated grain. In the United States, a family of 10 people was poisoned when they consumed meat from a hog who had ingested seed grain treated with methylmercury fungicide (Snyder, 1971). The mother of the family was in her second trimester of pregnancy at the time. Throughout the poisoning, the mother had no symptoms except slight slurring of speech. She had low mercury levels throughout exposure (peak=0.18ppm in urine). The infant, however, was born with a mercury level of 2.7 ppm. In Canada, 247 Cree Indian children were exposed to methylmercury in utero when their mothers ate contaminated fish (McKeown-Eyssen et al., 1983). Mercury levels in the hair of their mothers averaged at 6 mcg/g and only 6% had levels above 20 mcg/g.

Mutagenicity

Skerfving et al. (1974) reported an increased incidence of chromosomal aberrations in men who consumed fish contaminated by methylmercury. Popescu et al. (1979) also found an increased frequency of chromosomal aberrations in workers exposed to between 0.15-0.44 mg/m3 of mercury (4-10 times the present acceptable level in the U.S.) and who had urinary mercury levels averaging around 890 mcg/l. Some of these workers worked with organic mercury or elemental mercury and others were exposed to mercury vapor.

Male Exposure

No relevant data found.

Female Exposure

Many of the pregnant women in Iraq and Minamata experienced relatively mild symptoms such as parasthesias and occasionally visual symptoms such as visual field constriction, whereas their infants often had very severe symptoms accompanied by considerably higher levels of mercury. Two of the Iraqi mothers died a few days after delivering their infants (Amin-Zaki et al., 1979).

Placental transfer. Mercury and methylmercury readily cross the placental barrier. Fetal levels of mercury usually exceed the maternal blood level by a difference ranging between 10 to 15% (Lauwerys et al., 1978) to as high as 100% (Nishima et al., 1977; Tsuchiya et al., 1984) even after correcting for differences in hematocrit level (Amin-Zaki et al., 1976).

Mercury content is usually higher in the placenta than either maternal or fetal blood (Tsuchiya et al., 1984). Average placental mercury levels average over a wide range, 0.23-7.15 mcg/100g wet weight (Pitkin et al.,1975?6; Suzuki et al., 1971; cited by Roels et al., 1978).

The half-life for the excretion of methylmercury has been reported as long as 42 days (for lactating women) to 75 days (Greenwood et al.,.1978).

Breast milk. Pitkin et al. (1976) reported that women in Iowa City had average mercury levels in their breast milk of 0.9 mcg/l, whereas Fugita and Takabatke (1977) report mercury levels 4 times higher in Japanese women. Wolff (1983) calculated that mercury levels in breast milk in Iran and Minamata exceeded the maximum allowable concentrations by 7-135 times. She estimated that body burden of mercury in the infant could double during 4-40 days of breastfeeding.

Eight Iraqi infants exposed only to methylmercury through their mother's milk had mercury levels of about 200 ng/ml. Although initially these infants showed no signs of poisoning (Amin-Zaki et al. 1974), they subsequently demonstrated hyperreflexia, and delayed speech and motor developmen. Their symptoms appeared less severe than in infants exposed in utero (Amin-Zaki et al.,881979?). Mercury levels in breast milk fell between 5-9% of the concentration in maternal blood (Koos and Longo, 1976; Amin-Zaki,1976).

Pregnancy complications. In spite of relatively high levels of methylmercury exposure, pregnant women in Minamata and Iraq did not seem to suffer any undue complications during pregnancy. Most of the infants were born fullterm. Some of the Iraqi women had prolonged labor (Amin-Zaki et al., 1974). One woman in the Iraqi sample reported unusual vaginal bleeding in the first trimester.

Pregnancy outcome: Spontaneous abortion. Probably the earliest report of the reproductive hazards of mercury come from reports of women treated with mercury for syphilis and who later miscarried (Koos and Longo, 1976). Alonso and DeAlvarez (1960) reported a case of women who successfully induced a spontaneous abortion by the ingestion of mercuric chloride.

Bakir et al. (1973) noted that out of over 6000 cases admitted to hospitals in Iraq, only 31 were pregnant women. They estimated that about 150 women should have been pregnant based on population rates. Although Bakir et al. did not propose a reason for this low rate, it is possible that many of the women had been pregnant but had aborted early in their pregnancy without their awareness.

Neonatal health. Birthweight. The Japanese infants were emaciated (Reuhl and Chang, 1979). Decreased birthweight was also noted in the Soviet case (Bakulina, 1968) but not in the American case (Snyder, 1971).

Neonatal health: Congenital malformations. Mild to moderate microcephaly was reported in 5 of the 26 affected infants in Japan (Murakami, 1972), and 8 cases out of the 32 affected infants in Iraq (Amin-Zaki et al., 1979). Malocclusion (N=14), strabismus (N=13), and skull deformities (N=11) were noted among the 26 fetal Minamata victims (Murakami, 1972). The incidence of these malformations in the unexposed population of these countries is not known.

Neurodevelopment: Infant As in cases of adult intoxication, methylmercury has an affinity for the nervous system of the fetus. Cerebral palsy symptoms such as spasticity, and hyperreflexia are characteristic of in utero mercury intoxication. Other symptoms of the Minamata infants included lethargy, failure to follow visual stimuli, uncoordinated sucking or swallowing, and convulsions (Reuhl and Chang, 1979). Difficulty in sucking and swallowing was not noted in the Iraqi infants (Amin-Zaki et al., 1974) and difficulty in following visual stimuli was noted in the American case (Pierce, 1972)

In Iraq, 10 out of the 32 infants exposed in utero to methylmercury had signs of cerebral palsy, and 14 demonstrated hyperreflexia. Cerebral palsy was associated with high mercury levels in the mother's hair and with exposure in the third trimester (Amin-Zaki et al., 1979). Presence of psychomotor retardation was dose-related to levels of methylmercury in the fetus (Marsh et al., 1980). Abnormality of muscle tone and reflexes was dose-related to an index of prenatal mercury levels in Cree Indian children aged 12-30 mo. Hypotonicity was also reported in the case from the United States (Pierce, 1972).

The Iraqi infants were irritable (N=14), had exaggerated reactions to noise, cried excessively, and smiled, laughed or cried without provocation (N=8)(Amin-Zaki et al., 1979). Excessive crying and irritability were reported in 3 of the Japanese cases (Murakami et al., 1972) and in the case from the United States (Snyder,1971). The American infant had a weak and high pitched cry.

Eight children were blind or had impaired vision and 4 had impaired hearing (Amin-Zaki et al., 1979; Bakir et al., 1980). Hearing deficits and blindness were not noted in the Minamata infants, although constriction of visual fields was noted in some cases as the children grew older (Harada, 1976; Reuhl and Chang, 1979). By one year, the infant reported in the United States also was blind (Pierce, 1972).

Neurodevelopment: Childhood. As the children grew older, other deficits emerged. In Japan, many of the children showed other types of motor deficits such as marked incoordination with both spastic and flaccid paralysis,ataxia, dysarthria, and involuntary movements. Some lagged in motor and language development. Mental retardation (IQ of 75 or less) was noted in all 23 cases at Minamata Bay (Harada, 1977). Severe retardation was reported in 3 of the 10 cases in the Soviet Union (Bakulina, 1968) and in the Swedish case (Engleson and Herner, 1952). Bakir et al. (1980) considered 4 children of the Iraqi infants to have severe deficits in "mental power". Deficits in intelligence remained unimproved in 15 years of followup of the Minamata cases; however, motor function was somewhat improved in the children with mild deficits, although ataxia and speech disturbances persisted in almost all (Harada, 1977).

Two-thirds of the Jaspanese children had abnormal EEG recordings (Harada et al., 1971; see Kojima and Fujita, 1973). The American case (Snyder, 1971) had tremulous movements as an infant. Although at birth his EEG was normal, by 3 months it showed spike activity. By his 8th month, he developed myoclonic jerks and nystagmus.

Possibly even more than 23 children were exposed in utero to methylmercury at Minamata Bay. Harada (1976) reported that as many as 29% of children born in Minamata between 1955-1958 were mentally retarded, a percentage significantly higher than in age-matched populations. These mentally retarded children experienced sensory disturbances and clumsiness in fingers and other motor deficits.

In Iraq, most of the 23 children who lived (28% of the children followed died) had motor, speech, or mental developmental delays, and neurologic signs as Babinski reflex and hyperreflexia (Amin-Zaki et al., 1979). In United States, the infant could not sit up at 1 year (Pierce et al., 1972).

Infant mortality. Thirty- two of the infants exposed in utero in Iraq were examined over a five-year period (Amin-Zaki et al., 1979). Of the 14 children who initially had symptoms, 5 who had cerebral palsy died, and of the 18 children who were initially symptomless, 4 died. Infants who died had maximum maternal hair concentrations ranging between 147-500 mcg/g (Amin-Zaki et al.,1979).

Pathology reports. Investigators have examined the brains of 2 Iraqi infants who died (Choi et al., 1978) and of 2 Japanese infants (Matsumoto et al., 1964). The exposure ands disease course differed in the 4 cases. In the 2 Japanese cases who were both profoundly retarded, autopsy revealed general brain atrophy, with hypopklasia of the cortex, especially of the granular cell layer of the calcarine and the central gyri, and in the corpus callosum, Abnormalities were noted in cytoarchitecture. In the 2 Iraqi cases, abnormalities were found in the migration of neurons in cerebral and cerebellar cortices and in cytoarchitecture.

Comments

Because many of the metals have similar reproductive effects, their findings will be reviewed in this single section. Some metals have been consistently found to be mutagens to human somatic cells (arsenic, mercury), whereas others have been found less consistently to be mutagens (cadmium, lead). These findings are not necessarily indicative of the mutagenicity of these metals to reproductive cells.

Many of the metals (e.g., cadmium, mercury) and others which have not been reviewed here (e.g., copper), have been found to be good spermicides in in vitro experiments. Nevertheless, few studies have examined the effects of metal exposures on semen quality and fertility. Only boron and lead have been reported on. In exposures of both these metals, decreases in libido and sperm count have been noted. In addition, studies on workers exposed to lead have consistently shown decreases in sperm motility, and with relatively high exposure, increases in abnormal sperm.

Most metals cross the placenta faily easily; mercury probably crosses more easily than lead which in turn crosses more easily than cadmium. Since metals are also found in breastmilk, in utero exposures can be exacerbated by postnatal exposure.

Women whose partners have been exposed to metals (arsenic, lead) demonstrated slight nonsignificant increases in miscarriage rates, whereas women who were directly exposed to metals showed significant increases in miscarriage (arsenic, antimony, lead, mercury). Women who work with metals during pregnancy often have lighter babies (cadmium, mercury, and inconsistently for lead). There exists some evidence although not particularly consistent that lead exposure during pregnancy might be related to pregnancy complications. Pregnancy complications associated with other metal exposures have not been reported on. Lead and mercury have been associated with congenital malformations, but future investigations are needed to confirm these findings and to examine malformation rates associated with other metal exposures. Probably some of the most alarming effects of metals are on the neurodevelopment of the children exposed in utero. To date, only the neurodevelopmental effects of lead and mercury have been examined.

Many of the studies were based on workers exposed to metals while working for the metallurgy or smelting industries. Workers were often exposed to many different metals as well as other agents such as hydrogen sulfide and sulfur dioxide. For this reason, it is difficult to attribute the effects to any one exposure. Furthermore, many of the studies looked at rates of spontaneous abortion by comparing women's pregnancy outcomes before employment with those after employment. Parity and maternal age are important confounders when looking at rates over time, yet were rarely controlled or examined in the studies presented. As in many of the studies in this review, exposure levels were not reported.

Compared to other chemical exposures, there exist good and accurate biological indicators of metal exposures, such as, blood, urine, and hair levels. In fact, there exist so many indicators that it is often difficult to know what is considered toxic levels for that particular indicator; authors often did not provide this information. For some metals there is no agreement as to the units of measurement, e.g., methylmercury.

PESTICIDES

This section incorporates the reproductive hazards of specific pesticides and of agricultural chemicals, in general. Pesticides include herbicides, insecticides, and fungicides. Certain of these chemicals (e.g. kepone, DDT) are no longer available in the U.S. Nonetheless, we include these chemicals because of their similarity to chemicals still in use. Exposure to pesticides can occur during the manufacturing process, and throughout the distribution, sales, and final application.

Carbaryl

Carbaryl (1-naphthyl-N-methyl carbamate) is produced as an insecticide. Whorton et al. (1979) found that carbaryl-exposed workers showed only slight nonsignificant decreases in sperm count with a slight increase in proportion of workers who were oligospermic when compared to an historical control group.

Wyrobek et al. (1981) found in studying semen from 50 workers in the same cohort that there was a significantly higher proportion of morphologically abnormal sperm among the exposed compared to 34 unexposed, newly-hired employees. Workers who had previously been exposed to carbaryl an average of 6.3 years also showed a significant increase in sperm abnormalities compared to controls.

Dibromochloropropane (DBCP)

DBCP (1,2-dibromo-3-chloropropane) is a nematocide, widely used in agriculture in the United States and abroad from the mid-1950s until 1977. The discovery of its adverse reproductive effects in humans led to a partial U.S. ban on production. Prior to the ban, DBCP was used commonly on citrus fruits, grapes, peaches, pineapple, soybeans, and tomatoes (Whorton, 1982). Since 1979, its only allowed use in the United States is to treat pineapples in Hawaii (Whorton, 1982).

Mutagenicity

Evidence of cytogenetic change secondary to DBCP exposure was noted by Kapp and associates (1978). The sperm of 16 of 18 DBCP-exposed workers showed a statistically significant increased occurrence of Y-chromosome non-disjunction compared to a group of controls.

Male Exposure

Semen quality. Interest in the reproductive effects of DBCP was sparked in the late 1970s when DBCP production workers in a northern California chemical plant complained of inability to father children. Initial studies by Whorton et al. (1977) confirmed semen and hormonal abnormalities in 12 of the 25 who had not had vasectomies. Nine of the 12 exposed workers were completely azoospermic and 3 were oligospermic (sperm count greater than 0 and less than 20 million sperm per ml). Further, there was a direct relationship between sperm count and duration of DBCP exposure; all those with abnormally low sperm counts were employed for more than 3 years, whereas none of the normospermic employees showed more than 3 months of exposure. A subsequent study (Whorton et al., 1979; Milby and Whorton, 1980) of 154 DBCP-exposed and 42 non-exposed workers in this plant confirmed the original findings: 13.1% of the DBCP exposed workers were azoospermic, 16.8% oligospermic, and 15.8% had low normal sperm counts

(20-39 million sperm per ml). Contrasting figures for nonexposed workers were 2.9% azoospermic, 0.0% oligospermic, and 5.7% low normal. Median sperm counts for exposed workers were 46 million sperm per ml while the median for non-exposed workers was 79 million sperm per ml (statistical significance not calculated). The degree and length of exposure to DBCP was directly related to the level of sperm count depression.

Other studies have not confirmed the decreased sperm counts as being dose-related to DBCP exposure. One study of DBCP-production workers failed to show a large difference between sperm counts of exposed (59.5 million sperm per ml) and non-exposed workers(60 million per ml) (Lipshultz et al., 1980). However, sperm counts were examined more than 1 year after DBCP exposure. Although the groups did not differ in median sperm count, 21.9% of exposed workers had sperm counts less than 20 million vs only 10% for controls. A dose-response relationship between decreased sperm count and length of exposure was not seen in a study of 71 chemical workers (Lantz et al., 1981). None of these workers was exposed for longer than 30 months.

Studies of formulators, applicators, farmers, farm workers, and sales personnel have been more equivocal than those of production workers. Glass et al. (1979) in a cohort study of 96 pesticide applicators in California, were unable to relate clinical infertility and azoospermia to DBCP exposure However, some sperm count depression (average=21.9 million per ml) was noted in applicators with DBCP exposure of 2 months or more in the current year. Sperm morphologic changes were not related to DBCP exposure (Kahn and Whorton, 1980; Glass, 1980).

Compared to previous studies, Sandifer et al. (1979) found an even greater depression in sperm count among DBCP formulators and users compared with a control group of nonexposed persons. Six of 8 (75%) formulators and 13 of 43 (30%) DBCP users had counts below 20 million per ml, compared to only 15% of the control population. Sperm count depression was significant in formulators, custom applicators, farmers and farm workers. Data suggested a dose-relationship between sperm count and DBCP use.

Recovery of sperm count after DBCP-induced toxicity has been studied by several investigators in follow-up studies. One year after exposure ended, Whorton and Milby (1980) found 6 of 9 (67%) oligospermic males had regained normospermia; 2 of 9 (22%) had improved but remained oligospermic; and none of the 12 azoospermics showed any improvement. Eighteen to 21 months after exposure ended Lantz et al., (1981) found a 3-fold improvement in sperm density when compared to sperm counts only 1 to 6 months after exposure. Four years after exposure, Potashnik found that 4 of 13 (31%) originally azoospermic and 5 of 7 (71%) oligospermic men showed improved sperm counts (Potashnik, 1983). Five years after exposure, Goldsmith et al. (1984), found that 4 of 13 formerly azoospermic men had recovered spermatogenesis during this period.

Potency and libido. A few investigators observed qualitative changes in potency and libido. Potashnik et al., (1978) noted symptoms of impotence (1 worker) and decrease in libido (3 workers) in 4 of the 6 exposed factory workers they studied. Testosterone levels in these workers were normal. However, the same investigator presented contrasting evidence in a 4-year evaluation of 20 oligospermic and azoospermic workers (Potashnik, 1983). Even though 9 workers remained azoospermic and only 3 recovered to normospermia, all 20 denied impotence or decreased libido during the 4-year period.

Physiologic changes. Nearly all the studies reviewed found hormonal changes in DBCP-exposed workers. Generally, serum levels of follicle stimulating hormone (FSH) were abnormally increased in exposed workers (Potashnik et al., 1978; Potashnik et al., 1979; Egnatz et al., 1980). Lipshultz et al., 1980 found an increase in mean FSH level in over 200 exposed workers compared to unexposed. Furthermore, significant negative correlations have been shown between sperm count and serum FSH as well as LH (lutenizing hormone) (Sandifer et al., 1979).

Findings regarding lutenizing hormone levels have veried. Several authors have found higher mean levels of LH in exposed compared to unexposed workers (Egnatz et al., 1980; Whorton et al., 1977) and others have found normal levels (Potashnik et al., 1978; Potashnik et al., 1979).

In general, testosterone levels are unaltered by DBCP exposure (Potashnik et al., 1978; Sandifer et al., 1979; Potashnik et al., 1979). Testosterone levels were depressed in a study by Lantz et al., 1981.

Testicular change. Physical examination has revealed decreases in testicular size (Egnatz et al., 1980). Testicular biopsy showed histologic change in DBCP-exposed azoospermics (Lantz et al., 1981). Potashnik and colleagues (1979) found atrophic change in the seminiferous epithelium, no spermatogenic activity, and hyalinized tubules in 12 azoospermic workers. Biopsy studies of less severely damaged testicles showed decreased cellularity within the seminiferous tubules (Whorton et al., 1979). Severity of testicular damage appeared to correlate with length of DBCP exposure (Biava et al., 1978).

Hearn et al., (1984) looked for a possible increase in testicular and other cancer rates among 511 DBCP-exposed workers. This cross-sectional study showed no statistically significant increase in risk for male genital cancers.

Pregnancy outcome of female partner. Sex ratio imbalance among children of DBCP exposed workers has also been investigated. In a recent study, Potashnik, et al., evaluated the effect of paternal exposure to DBCP on sex ratios of children born to workers. Before exposure, 52.9% of the infants conceived were male; after exposure the figure was 35.2%. A statistically significant low rate of 16.6% males occurred in one group (Potashnik, in press). Goldsmith and coworkers (1984), over a five year period, monitored the pregnancy outcome of families of 30 DBCP-exposed production workers. These authors found a predominance of female children in the pregnancy outcome of wives of exposed males, a finding in line with evidence regarding Y-chromosome non-disjunction presented earlier.

Kharrazi et al., (1980) found an increase in the rate of spontaneous abortion in the wives of pesticide applicators occurring before their husbands' exposures to DBCP (6.6%) vs after exposure (19.8%). Pesticide applicators receive relatively low levels of exposure. However, Goldsmith et al., (1984) suggested that spontaneous abortion may be an outcome related to low rather than high level exposure.

Female Exposure

No relevant data found.

DDT

DDT (2,2-bis (p-chloro-phenyl)1,1,1-trichloroethane) is a pesticide used commonly around the world. It has not been used in the United States since 1972 when it was banned because of its wide-ranging ecosystem effects.

Mutagenicity

Mutagenic properties of DDT were studied in Brazil in 23 DDT production workers and 35 non-exposed persons (Rabello et al., 1975). Exposure levels were quantified by measurement of plasma levels of DDT and its metabolic products. This study showed a significantly higher frequency of lymphocytes with chromosomal abnormalities among workers with high plasma DDT levels.

Male Exposure

No relevant data found.

Female Exposure

Menstrual disorders. Chase et al. (1973) in a comprehensive study of the health effects of pesticide exposure of migrant farm workers noted that menstrual irregularities was the most frequent complaint of women seen in clinics for these workers. In women with these complaints, mean DDT levels were twice as high as in women with no menstrual problems. This level was not statistically significant.

Placental Transfer. Organochlorine pesticides have been shown to be absorbed and to persist in human fat. Abbott et al. (1968) measured levels of BHC, dieldrin, and DDT, in 1963-64 and 1965-67 in 247 adults and 44 stillborn or premature babies and infants. These authors found BHC, DDT, DDE (a breakdown product of DDT), and dieldrin at levels lower than the 1963-64 study showed. This study also showed that at birth, DDT concentration levels were one-third those of adults.

Radonski et al. (1971) measured levels of organochlorines in Argentinian newborns. Pesticides were detected in the newborn at a concentration of about 40% of the mother's blood level suggesting a retarded transmission.

Selby and coworkers (1969) studied organchlorine pesticide levels in maternal blood and placental tissue of non-occupationally exposed women. DDT, DDE, DDD, dieldrin, aldrin, BHC, lindane and heptachlor epoxide were found in the placental and maternal blood from 36 rural and 16 urban adult white Louisiana women. High levels of a particular pesticide in maternal blood usually corresponed to high but different placental levels.

Pregnancy apparently changes the pesticide storage characteristics of human fat tissue. Polishuk et al. (1970) showed that lower storage of DDT, DDE, BHC and dieldrin occurs during pregnancy. All pesticides found in adipose tissue in pregnant women were also found in maternal and fetal blood, suggesting placental passage.

Breast milk. DDT has been found as a contaminant in human breast milk in persons exposed both non-occupationally and occupationally (Wolff, 1983). No association has yet been found between milk concentrations and human health effects of DDT (Wolff, 1983). Siddiqui and coworkers (1981) studied the levels of various agricultural chemicals including DDT in the blood, breast milk, and cord blood or nursing mothers in India. Significant correlations were noted among maternal blood, breast milk and neonatal blood with regard to total DDT and BHC (also an insecticide) levels. DDT levels in milk were higher than in maternal blood and maternal blood levels were higher than cord blood levels.

In a study of 50 breast milk samples from non-occupationally exposed women in Norway in the mid 1970s (use of organochlorine insecticides was banned in Norway by 1970), all milk samples contained hexachlorobenzol, one or more types of BHC, DDT and DDE, with other insecticides found in varying numbers of samples (Bakken and Seip, 1976). These authors found no significant change in mean total DDT content of human milk in Norway since 1970 when organochlorine pesticide use was banned.

Curley and Kimbrough (1969) studied organochlorine pesticide levels in 5 pregnant women. Eight pesticides were detected with blood levels decreasing slightly but significantly 1 to 6 days post partum and milk levels showing great variation.

Pregnancy outcome: Spontaneous abortion. Evidence has not confirmed that DDT exposure is linked to fetal wastage. O'Leary et al. (1970), in a study of residents of Dade County where DDT was extensively used, found no difference between plasma levels of a DDT metabolite in women who delivered term babies compared to those who aborted.

Ethylene Dibromide (EDB)

Ethylene dibromide is used as a nematocide, an agricultural fumigant, and as an additive in leaded gasoline. Wong et al., (1979) studied the potential reproductive effects of workers in four different production facilities (N=297). Compared to expected birth rates from National Center for Health Statistics data, the workers and their spouses experienced no difference in 3 of 4 of the plants. The wives of the workers in the 4th plant had half the number of births. The reason for this difference was not immediately obvious since exposure levels did not vary greatly across the plants. Further, when the data from all 4 plants were combined, the ratio of observed to expected births was 62/77.18 or .80, which was not statistically significant.

Hexachlorobenzene

Hexachlorobenzene is an organochlorine fungicide used in the treatment of wheat, barley, oats and other grains for use as seed. Information on the effects of hexachlorobenzene exposure in humans comes not from studies of occupational exposure, but rather from an incident in Turkey where treated grain was consumed. Hexachlorobenzene exposure can also occur during the industrial production of chlorinated solvents and pesticides (Peters, 1976.

A variety of serious physiological symptoms occurred in adults who consumed the hexachlorobenzene-treated grain. Symptoms in adults and children were cutaneous, hepatic, arthritic, visceral, urinery, and neurological in nature. These symptoms as well as death occurred in infants who did not eat the grain, but rather were breastfed by their mothers who had eaten it. In Turkey, cessation of breastfeeding was associated with less rapid deterioration of health (Cam and Acquired, 1963). Indeed, infants who became affected with disease did so only after exposure through their mother's milk.

Kepone

Chlordecone or kepone is a chlorinated hydrocarbon insecticide related in chemical composition to mirex, endrin, dieldrin, heptachlor, and chlorophenothane or DDT. It was manufactured and used in the U.S. until 1975. Its most common use was as a pesticide in ant and roach traps.

Sperm count was found to be depressed, and sperm motility was reduced in 13 of 23 heavily exposed kepone production workers (significance level not stated) (Taylor et al., 1978). Abnormal sperm forms predominated in those studied (Cannon et al., 1978) and testicular biopsy in 3 exposed workers showed decreased spermatogenesis (Taylor et al., 1978).

2,4-D

2,4-D (2,4-dichlorophenoxyacetic acid), is an herbicide commonly used in agriculture and forestry. It is closely related to 2,4, 5-T in chemical structure.

A recent case report from Arkansas described multiple malformations including facial, digital and limb defects and severe mental retardation in a child born to parents both heavily exposed to 2,4-D while spraying trees (Casey and Collie, 1984). Exposure of the parents was prolonged and at high levels and occurred both through respiratory and cutaneous routes. Exposure to the mother occurred 7 hours per day, 6 days a week from 6 months before conception to 5 weeks after her last menstrual period when pregnancy was confirmed.

2,4,5-T and Dioxin

2,4,5-trichlorophenoxyacetic acid (2,4,5-T) is a chlorinated herbicide used commonly for weed control in the United States from 1948 into the late 1970s. It was used in farming, gardening, forestry, and for weed control along roadsides and railroad rights-of-way. 2,3, 7,8-tetrachlorodibenzo-p-dioxin (dioxin or TCDD) is a toxic contaminant of 2,4, 5-T and may be responsible for the toxic health effects of the herbicide. The combination of 2,4,5-T and TCDD or dioxin is often referred to as Herbicide Orange or Agent Orange. Agent Orange has been the subject of much recent study because of concern for human health effects of exposure that resulted from its use as a defoliant in South Vietnam. Many of these studies focus upon the compound Agent Orange rather than either of its two components, namely 2,4,5-T and dioxin. TCDD or dioxin is a condensation product of chlorophenols. Hence, it occurs as a contaminant in other compounds such as trichlorophenol.

Mutagenicity

Potential for mutagenesis has been studied among persons exposed to high concentrations of TCDD after a production accident in Seveso, Italy. Peripheral blood lymphocytes were studied from 69 controls, 59 workers, and 125 persons living near the plant. Although there appeared to be an increased frequency of aberrations in cells from the workers and neighboring residents compared to controls, the statistical significance of these results was not established (De Carli, cited in Pocchiari et al., 1979).

Male Exposure.

Semen quality. Sperm count and morphology were studied on 572 participants in the Air Force Health Study (Project Ranch Hand II), a government funded study of possible health effects from Agent Orange exposure in Vietnam veterans (Lathrop et al., 1984). There was no significant difference in sperm count or percent abnormal sperm between exposed and comparison subjects.

Infertility. As reported in the Air Force Health Study, there were no significant differences in a variety of fertility indicators including number of childless marriages, number of couples with desired number of children, and calculated indexes of fertility and infertility (married fertility index=no. of conceptions per years of marriage; total fertility index=no. of conceptions per years together; infertility index=no. of childless marriages per number of total marriages.

Potency and libido. Suskind and Hertzberg (1984) studied the long-term effects of 2,4,5-T and dioxin exposure on libido and potency in 204 production workers compared with 163 controls who were workers who had never been exposed to 2,4,5-T. The subjective complaint of loss of libido was noted by exposed persons more frequently. There was also an increase in complaints of impotence among the exposed group. However, when age was controlled for, the difference disappeared.

Pregnancy outcome of female partner. Townsend and coworkers (1982) studied the reproductive outcomes among wives of dioxin-exposed and non-exposed workers in a Michigan chemical plant. Paternal dioxin exposure was noted in 737 conceptions (370 women) compared to 2031 conceptions (345 women) with no exposure. There were no significant differences between reproductive outcome in the exposed group compared to the unexposed group. Participation rates for this study reflected only about 40% of the true exposed group.

Pregnancy outcome in wives after dioxin exposure to workers was also studied by Suskind and Hertzberg (1984). These authors found no differences between exposed and non-exposed groups in number of pregnancies, miscarriages, livebirths, stillbirths, and early neonatal deaths. In the Air Force Ranch Hand Study there was no significant difference between exposed veterans and controls in rates of premature births, miscarriage, stillbirth, livebirth, and induced abortion (Lathrop et al., 1984).

Smith and coworkers (1982) used data gathered by postal questionnaire to study miscarriage rates among wives of professional 2,4,5-T sprayers. A total of 548 chemical applicators and 441 controls responded to the questionnaire. There was no significant difference in risk of miscarriage for the sprayer's wives compared to the wives of non-exposed agricultural contractors.

Neonatal health: Congenital malformations. The Air Force Ranch Hand

Study found a significant difference between exposed and comparison groups for occurrence of minor birth defects such as birth marks, but no difference in occurrence of more severe defects (this data was from parental history and was not verified through medical records)(Lathrop et al., 1984). Unspecified physical handicaps in their children were also increased significantly for the exposed veterans in the Air Force Study. No differences were observed for prematurity, learning disabilities, or infant deaths.

Suskind and Hertzberg (1984) in their study of 204 exposed production workers and 163 controls found no differences between exposed and unexposed groups (data not verified) in birth defects. Townsend and coworkers (1982) studying the pregnancy outcome of wives of exposed workers found no significant differences in congenital malformations or health defects between exposed and controls.

An Australian case-control study of Vietnam veterans found no evidence linking army service in Vietnam to the risk of having a child with a birth defect (cited by Lipson, 1983). The relevance of this study to the effects of 2,4,5-T exposure has been challenged since Australian troops probably received little or no Agent Orange exposure in Vietnam.

Finally, a New Zealand study showed no elevation in frequency of congenital malformations in children of wives of exposed agricultural contractors vs wives of non-exposed agricultural contractors (Smith et al., 1982).

Infant mortality. Neonatal deaths were found to be significantly increased for the exposed veterans in the Air Force Ranch Hand Study (Lathrop et al., 1984). Suskind and Hertzberg (1984) found no differences between exposed production workers and controls in numbers of infant deaths (data unverified by medical records). Townsend and coworkers (1982) also found no significant differences in infant death rates between wives of exposed workers and unexposed controls.

Female Exposure

Pregnancy outcome: Spontaneous abortions. Studies following the Seveso contamination incident in Italy generally demonstrated that rates of spontaneous abortion were not significantly elevated in contaminated areas compared to uncontaminated areas after the incident (Reggiani, 1978). Analysis of aborted tissue in 30 cases where the pregnant women were exposed showed no developmental or chromosomal abnormalities (Rehder et al., 1978).

The so-called "Alsea" study conducted by EPA on spontaneous abortion rates in a 2,4,5-T sprayed area in Oregon led to an emergency suspension of use of that chemical. In this study EPA found a cluster of ten spontaneous abortions (3 would have been expected) during one month when 2,4,5-T was sprayed (cited by Clark, 1980). This study remains very controversial.

Neonatal health: Congenital malformations. Rates of congenital malformations in Seveso following the contamination incident showed no significant difference between contaminated zones compared to uncontaminated ones and no unusual clusters of specific malformations were noted (Homberger, 1979). Furthermore, after the incident, congenital malformation rates in the contaminated areas equalled the rates normally expected in Western nations (Pocchiari, 1979).

Several studies have evaluated possible health effects, especially congenital malformations, occurring among populations living in areas where 2,4,5-T is used as an herbicide. Hanify, et al., studied 37,751 babies born in Northland, New Zealand, from 1959 to 1965 when 2,4,5-T was not sprayed and from 1972 to 1976 when it was used. Incidence rates of birth malformations in these two groups were compared. A significantly greater number of cases of talipes malformations was noted in the period when 2,4,5-T was used (Hanify et al., 1981).

There is inconsistent evidence concerning the relationship of 2,4,5-T exposure on CNS defects. An ecologic study from Hungary showed no increase in incidence of central nervous system defects or other congenital defects with increasing 2,4,5-T use (Thomas, 1980). Hanify et al. (1981) in the New Zealand study also found no association.

Field and Kerr (1979) studied neural tube defects in one area of Australia and found a linear correlation between annual 2,4,5-T usage and rates of anencephaly and meningomyelocele (significance level not given). These authors also found a significant (level not stated) seasonal variation in births of babies with neural tube defects--although no causal connection is suggested, rates increased during periods of maximal 2,4,5-T use.

In contrast, 2 other studies found no association between 2,4,5-T exposure and CNS malformation. Brogan et al. (1980) confirmed a significantly higher incidence of cleft lip and palate defects from spring and summer conceptions compared to autumn and winter conceptions. Nelson and co-workers (1979) studied the relationship between cleft palate occurrence and use of 2,4,5-T in Arkansas from 1948 to 1974. In this ecological study, 1201 cases of cleft lip and/or cleft palate were identified. This study showed increasing incidence of facial clefts over the 26 year time span for the two groups defined as high-exposure and low-exposure, however, no dose-relationship between 2,4,5-T use and facial clefts was seen. The authors suggested that the increase may be due to better case reporting, not exposure to the pesticide.

Comments

Pesticides have been shown to have a variety of reproductive effects secondary to workplace exposures. The most striking reproductive effect has been sperm count depression and sterility in male workers caused by DBCP. DBCP has also been shown to effect mutagenic changes in sperm, hormone changes, testicular damage, abnormal sex ratios in children, and increased rates of spontaneous abortion. Carbaryl causes sperm morphologic abnormalities. DDT has been shown to cause somatic cell mutagenesis. DDT and hexachlorobenzene can be transferred through human breast milk. 2,4-D causes congenital malformations and 2,4,5-T causes increased neonatal death rates.

In general, few pesticides are well-studied. In some cases, there may be only one or a few human reproductive studies on a given pesticide. In most cases only one or a small number of outcome indicators have been studied for each compound. The outcomes that have been looked at are usually in males. There is a notable lack of data on reproductive effects of pesticide exposure to women workers.

There has been some effort to identify indicator tests (FSH level, for example), but this has achieved only moderate success. Indeed, it is interesting to note that with pesticides such as DBCP, for example, no health effects other than reproductive ones were found in exposed workers suggesting that the reproductive system itself may serve as an early indicator of chemical toxicity.

These studies generally do not provide good evidence of individual human exposure levels to a given pesticide. This makes the determination of a dose-response relationship or a no-effect threshold level from these studies an extremely difficult if not impossible task. Indeed, several studies have utilized aggregate, not individual, data. This is appropriate for early studies in an area, but not useful for deriving definitive conclusions about effect or causality. Exposure levels are difficult to secure in the pesticide field because of a lack of industrial hygiene data and inadequate long-term exposure records. It is even more difficult to gauge exposure in circumstances where exposure occurs outside the production site, for example, to the pesticide applicator or the person living near the sprayed area.

Adequate participation rates in studies has been a problem, especially in those where semen samples are required. Further, workers seem less than eager to participate when their reproductive lives have been completed. Also, studies that have gathered data through postal questionnaires have had difficulty securing adequate returns.

In general, though, the effort to identify reproductive effects of pesticides has gained considerable sophistication during the past 5 to 10 years, especially in designing ways to gauge individual exposures in the production facility itself and where exposure occurs on the job but outside of a confined workplace.

POLYBROMINATED (PBB) AND POLYCHLORINATED BIPHENYL. (PCB)

Polybrominated biphenyls (PBBs) and polychlorinated biphenyls (PCBs) belong to the class of halogenated aromatic hydrocarbons. They have been a valuable resource in industry because oftheir chemical stability, low volatility and nonflammability. (Letz, 1983). Yet, these same properties cause the persistence of PBBs and PCBs in the environment. They are a potential reproductive health concern to humans and animals because once absorbed they are poorly metabolized, slowly excreted and bioaccumulate in fatty tissue. (Rosenman 1979). Both chemicals have been banned in this country.

PBBs

Polybrominated biphenyls (PBBs) are compounds that were developed for use as a flame retardant in thermoplastic products (Rosenman et al., 1979). In 1973, PBBs were inadvertantly mixed into cattle feed in the state of Michigan leading to widespread contamination of the food chain (Kay, 1977). Most of the investigations on the health effects of PBBs have been generated from this incident.

Male Exposure

Semen quality. To date, only one human study has examined the effects of PBB on human spermatogenesis. Provoked by findings of a clinical field study of PBB-exposed men who complained of loss of libido (Anderson et al.,1978), Rosenman et al. (1979) studied the semen quality of farmers and individuals who had consumed food from PBB-contaminated farms, and PBB worker who may have inhaled or ingested the chemical. The results showed normal sperm counts, motility and morphology in these men compared with a control group of male university students. Men with possible confounding factors, i.e., varicocele and marijuana use, were eliminated. In concluding,the authors noted that the collection of sperm did not occur until 4 years after the contamination incident and therefore, the possiblity remains that an earlier PBB effect on spermatogenesis was reversed.

Female Exposure

Placental transfer. Eyster et al. (1983) obtained serum, placenta and cord blood samples, as well as tissue and milk samples from women giving birth. Cord blood and the placenta contained 1/10 maternal serum concentration, indicating that PBBs can cross the placenta, although not readily.

Breast milk . The lipophilic nature of PBB allows it to accumulate in maternal breast milk. A study by Brilliant and his coworkers (1978) indicated detectable levels of PBB in 96% of the 53 samples randomly collected in nursing mothers in Michigan's lower peninsula. The highest concentration was 1.2 ppm, and the median was 0.068 ppm. Because levels were so easily detectable in breast milk, the authors suggest that levels of breast milk could be substituted for measures of adipose tissue in the monitoring of women exposed to halogenated hydrocarbons. In another study, Eyster and coworkers (1983) found that milk levels in women living on PBB-contaminated farms was more than 100 times the maternal blood level, and measured approximately 8/10 the PBB level in adipose tissue.

Neurodevelopment. A number of studies have been conducted to assess the possible effect of PBB-exposure on the developmental abilities of young children (Weil et al., 1981; Seagull, 1983; Schwartz and Rae 1983). The studies examine children in Michigan who were exposed to PBB in utero; in early infancy, or both. A number of these children were breastfed by mothers who ingested PBB-contaminated foods.

Weil and his associates (1981), conducting the first investigation of this kind, failed to identify any significant effects of PBB on physical health and growth when 33 children, born on PBB-contaminated farms were compared to 20 unexposed controls. Psychological development testing also revealed negative findings. However, on several of the McCarthy Scales of Childrens' Abilities there was a significant inverse relationship shown between PBB fat level and performance. The fat levels of PBB, available for 27 of the children ranged from below 0.12 ppm to above 1.0 ppm. While more than half of the children were below the 0.1 level, only five children fell in the levels above 1.0 ppm. The mean age of the children was 37.2 months.

Seagull (1983) also found that children with higher fat PBB levels scored significantly lower the McCarthy Scales. The 19 children that she examined, ranging in age from 2 to 3 years, were divided into high and low exposure categories for the purpose of the study. No other comparison group was used. PBB fat values were between 21.0 and .010 ppm.

Schwartz and Rae (1983) further assessed 18 of these 19 children two years after Seagull studied them. Using McCarthy Scales and the Wechler Preschool and Primary Scale of Intelligence, the results of their follow-up cognitive testing indicated that the PBB-exposed children functioned within the normal range in all developmental areas. When comparing children with high vs. low PBB levels, only a nonsignificant difference in perceptual skills was observed.

PCBs

Introduced into industry in the 1930s, PCBs are manufactured commercially by the progressive chlorination of biphenyl in the presence of a catalyst (WHO 1976). PCBs are found in the heat exchange fluid of transformers and capacitators, hydraulic and lubricating fluids, plasticizers, printing inks and paints (Letz, 1983). PCBs enter the environment through the careless disposal of industrial fluids, and leakage of nonclosed systems (WHO, 1976). They have been found in samples of air, soil, and water, as well as in fresh fish in such areas as the Great Lakes (Jackson 1984). Since the 1977 ban on PCBs by the Environmental Protection Agency, the occupational and environmental exposure has been reduced (Letz 1983). However, NIOSH estimates that 12,000 workers are potentially exposed to PCBs (NIOSH, 1977, cited by Letz,1983). Large numbers of transformers and capacitators, long in use before the ban, still contain PCB fluid, and remain a hazard to utility workers, appliance service workers and firefighters (Letz, 1983).

Most of the epidemiologic literature on the subject is the result of an incident of PCB food contamination occurring in Japan in 1968. Called "Yusho," the Japanese word for rice oil disease, the episode involved the ingestion of cooking oil laden with PCB by some 1600 people (Kuratsune et al., 1972).

Female Exposure

Placenta transfer. In several studies, PCBs have been shown to cross the placental barrier (Jacobson et al., 1978; Yakushiji et al. 1978). Although one study (Yakushiji et al. 1978) found PCB levels in the placenta were almost equal to that of the maternal blood, blood cord levels have been found, generally, to be significantly lower than maternal serum levels. This suggests that the placenta functions as a partial barrier to the entry of PCB (Matsuda et al.,1978, as cited by Jackson 1984).

Breast milk . Several studies show PCBs have been transferred to infants from their mothers through lactation. (Yakushiji et al, 1198; Omeda et al., 1978; Kodama and Ota, 1980; Schwartz et al., 1983; Jacobson et al., 1984. In all of these studies, a higher content of PCBs were found in the milk as compared with maternal and cord serum. In one study in Japan (Kodama and Ota, 1980) serum PCB levels in breast-fed infants were significantly higher than PCB level in their mothers, 3 months post-partum. Although within a year, levels were four times the original cord levels in infants, after one year serum levels in the infants began to decline.

Neonatal health. A study on Yusho in Japan (Kuratsune et al., 1972) documents fetotoxic effects of PCBs in offspring of mothers who ingested PCB-laden rice oil. Ten of 13 babies had brown-stained or "cola" colored skin at birth, a high numbers of babies had eye discharge, and 12 of 13 babies were smaller than average. Elevated bilirubin, pigmentation of gums, nails, and groin, and hypoplastic deformed nails were also reported among babies in another study (Funatsu et al.,1971, cited by Rogan 1982). No physical or psychological disabilities have been noted in the follow-up of the children. Similar findings in babies born to women exposed of another PCB cooking oil contamination in Taiwan in 1979 have also been reported (Rogan 1979).

Comments

Overall, there is a dearth of information of the reproductive effects of PBB and PCB, most of which is derived from food contamination incidences rather than the workplace. In addition, many investigations have occurred years after the fact.

In studies on females both PBB and PCB have been shown to cross the placenta, although not readily. Levels of these agents, which are extremely fat soluble have been found in breast milk at up to 100 times maternal blood levels. There have been no accounts of increased pregnancy complications, including fetal loss. Lower birth weights and dermatological effects of PCBs were observed in offspring of women exposed in the Yusho oil contamination accident in Japan, but no persistent morphological or behaviorial effects have been documented. With PBBs there have not been reports of congenital malformations. Studies on the neurodevelopment of children expsed to PBB in utero are not consistent, although the most recent findings indicate that children are functioning within normal limits.

A single workplace study on the effects of PBBs on male spermatogenesis revealed negative findings. Given the persistence of PBBs and PCBs in the environment large scale epidemiologic studies on the reproductive effects workers exposed to these chemicals should be encouraged.

RUBBER

It is estimated that 500 or more chemicals are used in the production of rubber. In general, the toxicology of these individual chemicals as well as various combinations of them is poorly understood, although studies have shown some to be carcinogenic or mutagenic, especially those chemicals used as accelerators to speed the curing process and curing agents. Other compounds such as acrylonitrile, chloroprene, epichlorohydrin (see section), styrene and other solvents (see solvent section), vinyl chloride, carbon black, mineral oils, 1,3-butadiene, aromatic amines, and nitroso-compounds are also found in the rubber industry. The following section presents studies on both general rubber industry exposures and 1,3-butadiene and chloroprene.

General Studies

Mutagenicity

Maki-Paakkanen and coworkers (1984; Sorsa et al., 1983) studied chromosome abnormalities in the peripheral lymphocytes of 55 rubber workers and 35 controls at 2 different facilities. Rubber workers (mixers and weighers) who did not smoke had a significantly increased frequency of sister chromatic exchanges compared with office worker controls. A statistically significant difference in structural aberrations was seen in only one group of non-smoking workers, the weighers, in one of the 2 plants studied.

Falck (1983) studied the mutagenic character of the urine of 129 rubber workers and 54 controls in Finland and Sweden using a bacterial mutagenicity assay. The rubber worker's urine had higher mutagenic activity than that of the clerk controls. The chemical mixers, cleaners, vulcanizers, and tire builders had the highest levels of mutagenic activity. The author speculates this may be due to several factors including quantity and type of chemical exposures and inadequate use of protective gear. Urine samples tested after rubber workers returned from 4 weeks of vacation showed decreased mutagenicity and no detectable difference between workers and controls.

Male Exposure

No relevent data found.

Female Exposure

Pregnancy outcome: Spontaneous abortions. Two related studies have looked at spontaneous abortions and congenital malformations among women exposed to chemicals in the rubber industry (Lindbohm et al., 1983; Hemminki et al., 1983). Lindbohm and coworkers (1983) found that the rate of spontaneous abortion did not vary significantly for pregnancies occurring during employment compared with those before or after employment after adjusting for differences in age. However, in comparing frequency of spontaneous abortion for rubber workers with that for all Finnish women, Hemminki et al. (1983) found a small but nonsignificant increased frequency for rubber workers (rate of ab/preg)=7.4 for workers, 6.6 for Finnish women; ratio of ab/births=10.3 for workers, 8.9 for Finnish women). Rubber plant workers did, however, have slightly fewer abortions on average that the general community population surrounding the plant.

A case-control study of spontaneous abortions in a high exposure area of one plant, the footwear department, showed a ten fold increased risk of spontaneous abortion for women exposed to rubber chemicals to be significantly increased over that for unexposed women working in a nearby area of the plant (Lindbohm et al., 1983). Axelson et al. (1983) in a study of an apparent "cluster" of reproductive problems among a group of workers found a significant increase in pregnancy complications including miscarriages and threatened abortions among tire builders.

Neonatal health: Congenital malformation. Lindbohm and colleagues (1983) studied congenital malformations among children born to rubber workers. Infants with congenital malformations when matched to normal infants were not more likely to have mothers who worked for the rubber industry.

1,3-Butadiene

1,3-butadiene is a component of the manufacture of rubber, latexes, and resins. Although data does not exist showing human reproductive effects of 1,3-butadiene, NIOSH considers the substance a possible reproductive hazard because animal studies have shown maternal and fetal toxicity, teratogenicity, and testicular and ovarian atrophy (NIOSH, 1984).

Chloroprene

Chloroprene (2-chlorobuta-1,3-diene) is a monomer used in the manufacture of synthetic rubber and latex. A Russian study of chloroprene's mutagenic potential showed an increased level of chromosomal aberrations in the peripheral blood lymphocytes of 28 female workers exposed for 1-20 years compared with 181 non-exposed workers (Sanotskii, 1976). Animal studies of low-level chronic exposures have shown depressed fertility in males, evidence of mutagenicity and teratogenicity, and increased fetal death (Sanotskii, 1976).

Ethylene Thiourea (ETU)

Ethylene thiourea is a rubber accelerator, used to speed the curing process in rubber manufacture. In a 1976 study of formerly ETU-exposed female employees (exposure ended in 1972), Smith found no increase in congenital anomalies including congenital hip dislocation, tracheo-esophageal fistula, cleft palate, and congenital heart disease, among exposed workers compared with the reference group.

Comments

Studies of exposed rubber workers have shown somatic cell chromosomal abnormalities, mutagenic substances in their urine, and an increase in rates of spontaneous abortion in women working in the industry.

In general, the range of possible reproductive hazards caused by exposures in the rubber industry has not been comprehensively studied. Few outcome variables for either sex have been studied.

Further, studies have not attempted to separate or to measure chemical exposures, although efforts have been made to identify specific work areas where greater exposures probably occur. Although accurate individual exposure estimates are difficult to make in an environment such as a rubber plant, evidence from reproductive as well as other studies suggests that the level of harm from chemical exposure may vary greatly throughout the plant making such determinations very important.

ORGANIC SOLVENTS

Carbon disulfide and the aromatic solvents will be discussed in this section; for further information on solvents see Pesticides (hexachlorobenzene), Anesthetic gases (halothane and other halogenated hydrocarbons), Sterilizing agents (formaldehyde), Industry studies (laboratory workers), and Transplacental carcinogenesis (hydrocarbons).

Aromatics

Organic solvents that belong to the aromatic family include benzene, toluene, xylene, and styrene.

Mutagenicity

Cytogenetic studies of cultured lymphocytes have revealed increased rates of chromosomal aberrations and sister-chromatid exchange in workers exposed to greater than 25 ppm of benzene for periods of 1-26 years (Tough et al.,1965; Forni et al., 1971; Funes-Cravioto et al., 1977; Watanabe et al., 1980). Chromosomal aberrations have also been found in workers exposed to styrene (Meretoja et al., 1977), and inconsistently found in toluene-exposed workers (Forni et al., 1971; cited in Funes-Cravioto et al., 1977). However, in vitro studies demonstrated that toluene and xylene do cause significant cell-growth inhibition (Gerner-Smidt and Friedrich, 1978). Chromosomal breaks and increased frequency of sister chromatid exhange have been reported in children of women exposed to organic solvents in laboratories (Funes-Cravioto et al., 1977).

Male Exposure

Semen quality. As part of a NIOSH health hazard evaluation, semen quality was examined in workers who were exposed during the production of toluene diisocyante and polyurethane plastics to two toluene derivatives, dinitrotoluene (DNT) and toluene diamine (TDA)(Hamill et al., 1982). The preliminary studies by NIOSH uncovered a lower sperm count in 9 exposed-workers compared to 9 control workers. DNT concentrations ranged between 0.013-0.42 mg/m3 and TDA ranged between 0.008 to 0.39 mg/m3 (OSHA standard for DNT=1.5 mg/m3; no standards for TDA). Subsequent studies commissioned by the industry found no differences in sperm count and morphology between 59 exposed men (59% of possible participants) and 91 not exposed or slightly exposed workers (76%). The authors report no differences between groups in fertility history or in FSH levels. Exposure levels had decreased substantially in the followup survey to 0-0.10 mg/m3 for DNT and 0-0.04 mg/m3 for TDA (Ahrenholz, 1980).

Potency. Sabroe and Olsen (1979) reported complaints of impotence by furniture lacquerers in Denmark exposed mainly to toluene and xylene as well as to ketones (methyl ethyl ketone, methyl isobutyl ketone) and various alcohols (ethanol, propanol, butanol). Lacquerers who have not lacquered for an average of almost 10 years also complain of impotence but to a lesser extent.

Neonatal health. In a Danish case-control study, infants with central nervous system (CNS) malformations were 2.8 times (non-significant) more likely to have fathers who worked with a variety of organic solvents and 4.9 times more likely to have fathers who were painters compared to infants with other malformations (Olsen, 1983).

Female Exposure

Menstrual disorders. Russian, Polish and Indian investigators have described menstrual irregularities in women exposed to mixed solvents containing toluene (Michon, 1965; Syravadko et al., 1973; Matsushita et al., 1975; cited by Cohr and Stokholm, 1979). One Soviet study compared 110 women working in a plastics factory who were exposed to "low" atmospheric concentrations of styrene with 231 child-care workers (Zlobina et al., 1975). They found a nonsignificant increase in disorders of the menstrual cycle and in menstrual flow. The frequency of these disorders increased with age of the women and with years of working with styrene.

Pregnancy complications. The Soviet study by Zlobina et al. (1975) also demonstrated a significantly greater frequency of toxemia in 67 styrene-exposed women compared to 70 nonexposed women. A preliminary investigation has revealed the women exposed to a variety of organic solvents (n=90) are more likely to suffer from toxemia and hypertension during pregnancy than a group of pregnant control women (n=180) (Eskenazi et al., unpublished data).

Pregnancy outcome. Hemminki and coworkers (1980) reported almost a three-fold increase in the crude rate of spontaneous abortions (90 pregnancies) in women exposed to styrene during the production of reinforced plastics compared to the general population of Finnish women. A subsequent Finnish study on a much smaller sample of lamination workers (12 pregnancies) could not confirm these findings. The 67 lamination workers when compared to 67 food-production controls (matched in age and socioeconomic status) did have significantly fewer births; the authors suggested that a difference between groups in the number of induced abortions might explain these findings (Härkönen and Holmberg, 1982).

Neonatal health: Birthweight. In a preliminary investigation, Olsen and Rachootin (1983) reported no significant association between birthweight and exposure of either parent to a variety of organic solvents (in a variety of occupations). Birthweight was adjusted for birth length and potential confounders, such as, maternal age, smoking, alcohol consumption, and time needed to conceive were controlled for in the analysis. Exposure was defined as during any time "in the period prior to delivery". Using occupational information reported via a mail questionnaire, only 41 women were considered exposed in the year of their delivery

Neonatal health: Congenital malformations. Toutant and Lippmann (1979) suggested that a fetal solvent syndrome may exist. They described an infant with the classic facies, poor suck, jerky uncoordinated movements, and growth retardation (low birth weight and length) of an infant with fetal alcohol syndrome. The mother of this infant, however, drank little but was an addicted glue-sniffer (toluene). In two other case reports, women working with a mixture of solvents containing toluene (Mean daily dose=372 mg/kg) and trichloroethylene (405mg/kg) delivered infants with multiple malformations (Euler, 1967; cited by Cohr and Stokholm, 1979).

In utero exposure to organic solvents has been associated with an increased risk for malformations of the CNS and for cleft lip and palate. For example, 5 of the 9 infants born with sacral agenesis (failure of the lower part of the spinal column to close) between 1959-1966 in

Czechoslovakia, had been exposed in utero to various organic solvents (trichloroethylene and acetone, methyl chloride, xylene, acetone and petrol, and unspecified solvent)(Kucera, 1968). In a case-control study of infants born with congenital malformations of the CNS (40% anencephalic) and controls matched for time and place of delivery, Holmberg and Nurminen (1980; Holmberg, 1979) found that case-mothers are 4 times more likely (12 case-mothers vs. 3 control-mothers) to have been exposed to at least one of 12 different organic solvents. Differences between groups in maternal smoking are controlled for in the analysis, but it is not clear whether the authors controlled for differences other risk factors for CNS malformations such as parity and maternal age (Shiekh, 1979). Additional exposure to dusts had a synergistic effect. This finding was in accordance with the increased incidence of CNS malformations seen in children whose fathers are painters (see male exposure)(Olsen, 1983).

Using the Finnish Registry of Congenital Malformations, Holmberg and coworkers (1982) identified 388 infants born with cleft lip and palate. They compared the occupational and environmental exposures of 378 mothers of these infants with an equal number of mothers of normal children matched for time and place of birth. They found that exposure to organic solvents in the first trimester was more common for mothers of cases (n=14 exposed) than for mothers of controls (n=4 exposed).

Carbon Disulfide

Carbon disulfide (CS2), a man-made colorless solvent, was formerly used in the production of matches, fats, lacquers, and camphor, and in the refining of petroleum jelly and paraffin. Today, most of the occupational exposure to CS2 occurs during the manufacture of viscose rayon (spinning), and in the cold vulcanization of rubber (Davidson and Feinleib, 1972)

Male Exposure

Semen quality. A Rumanian investigation revealed reductions in sperm counts and altered sperm morphology in workers occupationally exposed to CS2 (Lancranjan et al., 1969; Lancranjan, 1972). Lancranjan and coworkers compared semen samples of 133 CS2-poisoned workers with polyneuritis, 140 rayon spinners with less exposure to CS2 (average exposure= 40 mo), and 50 unexposed workers at the same factory. They found that the semen of CS2-poisoned workers had a significantly greater number of abnormal sperm, lower sperm motility, and lower sperm count than that of unexposed controls. Complaints of decrease in libido, and sexual difficulties (erection and ejaculation) increased with extent of exposure (no significance levels were provided). They also found a significant decrease in ketosteroids in both patient groups and abnormal gonadotropin levels in 85% of the group with abnormal semen. A followup study revealed that the semen quality of 66% of 18 poisoned workers returned to normal after 3-30 months away from the toxic environment. Based on the hormonal studies, the authors concluded that CS2 attacks both the gonads and the hypothalamus.

The findings of a NIOSH investigation failed to confirm the findings of Lancranjan and coworkers (Meyer, 1981). As part of a NIOSH health evaluation survey (Meyer, 1981), semen quality of 86 men exposed to CS2 were compared to that of 89 men in the same plant not exposed to CS2. These men represented only 40% of the potential participants. The nature of their work, the type of plant, and the levels of exposures were not discussed. The results indicate that the CS2-exposed men when compared to controls have on average nonsignificantly higher sperm counts and equal numbers of abnormal forms. The authors suggest that the poor rate of participation limits the interpretation of the results.

Pregnancy outcome of female partner. Hemminki and Niemi (1982) reported increased rates of spontaneous abortions in wives of men who work in a viscose rayon plant compared to that of wives of all industrial workers in a Finnish community (rates of 14.9 and 7.6, respectively).

Female Exposure

Menstrual disorders. For over a century, women exposed to CS2 in the workplace have reported menstrual disorders (Delpech, 1856; cited by Cai and Bao, 1981; Cai and Bao, 1981). These disorders have included delay in menarche (Sarai, 1936; cited by Cai and Bao), amenorrhea (Sarai, 1936; cited by Cai and Bao, 1981), dysmenorrhea (Cai and Bao, 1981), and scanty as well as increased menstrual flow and duration (Bezvershenko, 1967; Vasiljeva, 1973; cited by Cai and Bao, 1981). In East Germany in the 1950's, the employment of women in a viscose rayon factory was discontinued when a severe increase in menstrual bleeding was noted in many women within 6 months of their employment (Ehrhardt, 1967). Menstrual disorders are often dose-related to the extent and years of exposure (Bezvershenko, 1967; Vasiljeva, 1973; Agadzhanova, 1978; cited by Cai and Bao, 1981).

Infertility. Women exposed to levels above 10 mg/m3 of CS2 have experienced difficulties in conceiving, especially if exposed for longer than 10 years (Agadzhanova, 1978; cited by Cai and Bao, 1981).

Placental transfer and breastmilk. CS2 readily passes through the placenta and has been detected in breast milk as long as 56 days after exposure and in the urine of breast-fed babies (Cai and Bao, 1981).

Pregnancy complications. In a study done in a rayon factory in China, Cai and Bao (1981) found that 12.7% of 79 pregnant workers exposed in the spinning process compared to only 3.6% of 84 controls (finishers) demonstrated toxemia. . Exposure levels in this factory ranged between 37 and 56 mg/m3. A previous study also found a three-fold risk for toxemia even at lower levels of exposure (10-60 mg/m3) (Agadzhanova, 1978; cited by Cai and Bao, 1981).

Pregnancy outcome. The Chinese study found no significant differences in the number of miscarriages or premature births. A Finnish study (Hemminki and Niemi, 1982) also found only a slight nonsignificant elevation in miscarriage rate for women working in a rayon factory (10.3%) compared to other women in the community doing industrial work (7.7%). No occupational levels of exposure were given. However, Hemminki and coworkers in an earlier study observed that women working in rayon factories were more than twice as likely to abort than the general population of Finnish women (Hemminki et al., 1980). Moreover, Petrov also (1969; cited by Cai and Bao) noticed that pregnant women exposed to 30 mg/m3 of CS2 were twice as likely to spontaneously abort and three times more likely to deliver prematurely.

Glycol Ethers

Two glycol ethers, ethylene glycol monomethyl ether and ethylene glycol monoethyl ether are strong organic solvents whose adverse reproductive effects have been investigated primarily in animals. Also know as 2-methoxyethanol (2ME) and 2-ethoxyethanol (2EE), they are colorless liquids whose applications vary from perfume fixatives to jet deicing additives (Cook et al., 1982). In 1983, some 220 million pounds of these substances were produced (Wall St. Journal, 1984). NIOSH estimates that as many as 500,000 workers are potentially exposed to these glycol ethers in manufacturing operations as well as in the formulation of the products that contain them (NIOSH Current Intelligence Bulletin 39, 1983).

Animal Studies

Evidence of adverse reproductive effects in animals have lead to recent changes by manufacturing companies in permissible exposure levels of glycol ethers (Wall St. Journal 1984). For 2ME, studies of pregnant female mice, rats, and rabbits have revealed significant increases in fetal deaths, major and minor fetal abnormalities, and maternal deaths. In male animals, investigators have described testicular atrophy, microscopic testicular damages, temporary infertility and abnormal spermhead morphology. Exposure of male and female animals to 2EE has revealed similar outcomes. The exposures were administered through different routes and at various concentrations. The effects appeared to be dose-related. Some effects were present at doses below the current OSHA standard of 200ppm (NIOSH Current Intelligence Bulletin 39, 1984).

Male Exposure

Infertility. A single human study (Cook et al. 1982) has examined the effect of 2ME on human male reproduction. This cross-sectional epidemiologic study of glycol ether manufactoring employees in Michigan revealed no evidence of decreased fertility when clinical analyses of semen and hormône levels were performed. However, testicular size was found to be significantly smaller among those men highly exposed to 2ME as hour time weighted average for 2ME was 0.042 ppm.

Female Exposure

No relevant data found.

Comments

Over 10 million workers are exposed daily to organic solvents, yet comparatively few studies have examined the reproductive effects of solvents. Furthermore, of the studies conducted, many of the adverse outcomes are inconsistently reported.

Some of the aromatics may be mutagens (benzene, styrene) but for others it is less clear (toluene and xylene). It is unclear whether solvents affect male fertility and semen quality. Single studies on CS2, TDA and DNT, and 2ME have reported significant changes in semen quality or testicular size; other studies could not confirm these findings or as of yet, have not been conducted (2ME). Studies reported that wives of workers exposed to CS2 have an increased rate of spontaneous abortions and that male painters exposed to aromatic solvents were more likely to have children with congenital malformations; no other studies have looked at these outcomes in wives of other solvent workers.

Findings in female workers are also unclear or inconsistent: increased or decreased menstrual flow has been consistently associated with CS2 exposure, nonsignificantly increased with styrene exposure, and casually observed for toluene exposure. Incidence of spontaneous abortions have been more often than not associated with CS2 exposure and inconsistently associated with styrene exposure. Three studies have reported increased incidence of toxemia in solvent-exposed women (CS2, styrene, mixed solvents). A number of studies have suggested that children of solvent-workers were more likely to have congenital malformations with 3 studies implicating malformations of the nervous system. One study implicated the existence of a fetal solvent syndrome similar in nature to the fetal alcohol syndrome. Alcohol is a solvent and therefore, a solvent syndrome is plausible.

With the exception of only a few studies, all of these studies have been conducted abroad and many of them have not been published in English. Many of the studies have not provided exposure levels and only a few provided biological indicators of exposure. Accurate biological indicators of most solvent exposures such as urine or blood levels, unlike for most metal or pesticide exposures, can only be obtained soon after exposure. Many of the workers were exposed to many other solvents and often to many other chemicals. Little is known about the synergistic effects of multiple exposures. Inconsistency in results may be due to differences in exposure levels across studies.

Studies on the neurotoxicology of solvents have suggested that there may exist a synergistic relationship between alcohol use and solvent exposure yet no studies on the reproductive hazards of solvents have controlled for alcohol use. Other confounders have rarely been controlled and therefore, most of the reported results are based on crude estimates.

VINYL CHLORIDE

Polyvinyl chloride (PVC) occurs in a wide variety of commercial products including clothing, upholstery, flooring, wire insulation, food containers, and phonograph records. There are several intermediate processes involved in the manufacture of polyvinyl chloride including the production of vinyl chloride monomer (VCM), polymerization of the monomer into polyvinyl chloride, and finally, fabrication of the PVC into products. Exposure to the vinyl chloride monomer, generally in the polymerization industry, is considered the most hazardous (Jones, 1981).

Mutagenicity

A number of studies have shown an increase in chromosomal aberrations in somatic cells of workers exposed to vinyl chloride. Purchase and co-workers (1978) reported an increased incidence of chromosomal abnormalities in the lymphocytes of 57 vinyl chloride workers compared to 24 controls. This study demonstrated a positive correlation between chromosomal damage and both length of exposure and exposure level. Autoclave workers with highest estimated exposure levels (>5ppm) had the greatest number of significantly increased abnormalities. Several other studies have shown a significantly higher incidence of chromosomal abnormalities among vinyl chloride exposed workers compared with non-exposed controls (Ducatman et al., 1975; Funes-Cravioto et al.,1975; Szentesi et al., 1976). Heath and Dumont

(1977) found an increase in chromosomal damage, but were unable to relate the increase to exposure levels. These authors found no difference between three industry groups (high VCM exposure, low VCM exposure, and no VCM exposure--control), however, there were differences between these three groups and an outside control group.

A follow-up study provides evidence that somatic cell chromosomal damage may be reversible. An earlier study of 39 PVC workers and 16 controls showed an increase in chromosomal breakage among the exposed workers. In the follow-up, undertaken 24-30 months after vinyl chloride exposure had decreased, there were no differences in lymphocyte chromosomal aberrations in workers compared to controls (Hansteen et al., 1978). A similar study found a reduction in lymphocyte chromosomal damage accompanying decreased vinyl chloride exposure after 42 months of decreased exposure, but not after 18 months. Exposures varied from an estimated high of 50 ppm during the initial study to less than 5 ppm during follow-up (Anderson, et al., 1980).

Several studies conflict with these findings and have shown no mutagenic effects of vinyl chloride (Fleig and Thiess, 1974; Killian et al., 1975). Although Fleig and Theiss (1978) showed an increased rate of chromosomal damage in workers with relatively higher exposures (10 to >100 ppm, 4 to 30 years) and showing symptoms of vinyl chloride illness, they did not find chromosomal abnormalities in less-exposed workers (1 - 30 ppm, 4 to 26 years). Picciano et al. (1977) studied 209 vinyl chloride workers whose exposure ranged from 1 to 332 months (average=48.3 months) and compared their rate of chromosomal aberration to 295 newly employed workers. These authors found no major differences in numbers of chromosomal aberrations between the exposed and non-exposed workers.

The discrepant findings of chromosomal damage related to vinyl chloride exposure may in part be explained by a possible threshhold level of exposure to vinyl chloride below which chromosomal damage does not occur and above which it does. Exposure levels are not always accurately known or given in many of the studies discussed above. Thus, exposure variation may account for the differences in findings.

Male Exposure

Pregnancy outcome of female partner. Infante and coworkers (1976) studied pregnancy outcome among the wives of 95 vinyl chloride-exposed workers. This study showed a statistically significant excess of fetal loss after husbands had vinyl chloride monomer exposure where no difference was seen before exposure. Adjusted fetal death rates before employment (pre-exposure for the study group) were 6.9% for controls and 3.1% for the study group. After employment (post-exposure for the study group), the comparable rates were 6.8% for unexposed controls and 10.8% for the exposed group. These figures are adjusted for age differences between the two groups. The greatest source of this effect occurred in pregnancy outcome associated with husbands younger than 30 years old.

Female Exposure

Neonatal Health: Congenital malformations. Early evidence that exposure to vinyl chloride may cause birth defects was detected in a study by Infante using aggregate data (Infante, 1976). He found that congenital malformations occurred at a significantly greater frequency in 3 Ohio cities that housed polyvinyl chloride production facilities compared to the rates statewide. Defects of the upper alimentary tract (RR=2.48), genital organs (RR=1.90), club foot defects (RR=2.79) and defects of the central nervous system (RR=3.02) such as anencephaly, spina bifida and hydrocephalus, were observed to be significantly increased.

One Ohio city, Painesville, with two polyvinyl chloride plants, showed an even more substantial increase in central nervous system (CNS) malformations. Scientists from the Centers for Disease Control used Birth Defects Monitoring Program (BDMP) data to compare CNS malformation rates in Painesville and a Pennsylvania community with a PVC plant with statewide rates (Edmonds et al. 1975). The study found no increase in CNS malformations in the Pennsylvania community, but an increase was shown in the Painesville area, primarily in anencephaly and spina bifida. A follow-up case-control study composed of a small sample (cases=15; controls=30) failed to show an association with vinyl chloride exposure.

BDMP data was also used to identify Kanawha county, West Virginia, as a community with a polyvinyl chloride facility and a significantly increased rate of CNS defects compared with the remainder of the United States (Edmonds et al., 1978). In a follow-up case control study (Edmonds et al.,) 46 cases with CNS defects were matched with 2 normal controls each. The study found no evidence that higher CNS rates in Kanawha county were related to parental exposure to vinyl chloride monomer.

Comments

Vinyl chloride has been shown to be mutagenic, and to be associated with increased rates of fetal death after paternal exposure and possibly CNS malformations following maternal exposure.

Less attention has been devoted to other reproductive effects such as male fertility. Studies of female exposure have been limited and tended to focus on environmental rather than workplace exposure and to utilize aggregate rather than individual data.

The studies of vinyl chloride do provide exposure levels, at least on an industry-wide basis. However, the extent and type of exposure varies widely with different production facilities and processes utilized. Discrepancies between results may occur because of differences in exposure levels across studies and in the differences of other exposures when producing vinyl chloride such as organic solvents.

Controversy exists about evidence linking vinyl chloride exposure to an increased risk for congenital malformations. The studies showing an increased risk have used registry, not individual, data. The findings of these studies have not been confirmed by follow-up case-control studies. However, in both follow-up studies, the numbers of cases were small.

MISCELLANEOUS CHEMICALS

Para-Tertiary Butyl Benzoic Acid (p-TBBA)

p-TBBA is an organic acid used in making paints and cutting oils. Interest was raised in p-TBBA because a study of cats fed high doses of the chemical developed testicular atrophy and seminiferous tubule degeneration. Lower doses also caused testicular damage in the rat (cited by Whorton, 1981). Whorton and coworkers (1981) studies male workers involved in p-TBBA production in a California chemical plant. Of a total of 115 workers, 51 provided semen samples. In comparing this group to an external control group of nonexposed men, no differences were found in sperm count or in the proportion of men who were oligospermic.

Bromide

A case report (Margurten et al., 1982) suggested that maternal exposure to bromide in a photographic lab may be associated with minor congenital malformations in the offspring. The mother had worked with photographic developing chemicals from the onset of pregnancy until several weeks before delivery. Maternal serum bromide levels were 15-29 mg/dl at delivery. The infant weighed 2920 gm at birth. She was initially cyanotic and hypotonic. She showed an increased inner canthal distance, broadening of the nasal bridge, and a dull, fixed facial expression. At 9.5 months, the infant showed some residual mild hypotonia of the neck, but was normal in her speech and social development.

INDUSTRY STUDIES

Agricultural Workers

A series of studies have looked at the effects of agricultural chemicals upon reproductive capacity. These studies do not attempt to specify individual chemicals.

Mutagenicity

Yoder and co-workers studied lymphocyte cultures from 42 pesticide applicators and 16 controls to evaluate chromosomal characteristics. During the heavy spraying seasons there was a increase in the frequency of chromosomal abnormalities, especially in those workers with heavy herbicide exposures (statistical significance not given) (Yoder et al., 1973). Impaired spermatogenesis, chromosomal breakage, and Y-chromosome damage were all noted in 5 insecticide workers studied by Shabtai et al. (1978) in Israel.

Male Exposure

Infertility. Shabtai and coworkers (1978) noted that the 5 men with chromosomal damage and Y-chromosome damage were infertile and all had been frequently exposed to various chlorinated and phosphate organic insecticides.

Potency and libido. In an early series of case reports, Espir and coworkers (1970) described a team of 5 chemically-exposed farm workers, 4 of whom had become impotent. This was no accompanied by a decrease in libido. When contact with the chemical was stopped and hormone therapy given, the 4 workers recovered sexual functioning.

Pregnancy outcome of female partner. A questionnaire survey was used to gather information on pregnancy outcome from wives of 314 agricultural pilots exposed to pesticides and 178 unexposed controls (Roan et al., 1984). The study showed no difference between the two groups in total pregnancies, sex ratio of children, children per couple, spontaneous abortions, and birth defects. Response rates for the survey were less than 40%.

Gordon and Shy (1981) used a combined ecologic (aggregate data analysis) and case-control methodology to study the relationship between agricultural chemical use and the incidence of congenital malformations in Iowa and Michigan. The study identified all cases of cleft lip and/or cleft palate in these two states during 1974 and 1975 and compared them with 671 controls. The cases were then classified by potential exposure to agricultural chemicals. The analysis showed an increased number of cleft lip and palate in areas with high exposure to a set of "suspect" agricultural chemicals, including insecticides, fungicides, herbicides, and defoliants.

Female Exposure

Neonatal Health: Congenital Malformations. Hunt and Harkness (1980), in the Collaborative Perinatal Project population, identified pesticide exposure in women as strongly correlated with the number of stillbirths and fetal deaths, premature low weight babies with low 5 minute Apgar scores, suspected neurologic abnormalities at 1 year, and low IQ ratings at 4 years. All socioeconomic and racial groups were affected comparably.

Laboratory Workers

Laboratory workers may be exposed to a variety of different chemical and biologic substances including reagents and solvents, infectious agents, dyes, and radioactive materials (Yager, 1973). A number of studies have attempted to identify reproductive hazards in women working in laboratories.

Mutagenicity

Funes-Cravioto and colleagues (1977) found a significant increase in chromosomal abnormalities in lymphocytes of 73 workers in laboratories and the printing industry (exposure to solvents) compared to 49 controls. Further, an increase in chromosomal abnormalities was also found in 14 children of 11 women who had worked in laboratories while pregnant.

Male Exposure

No relevent data found.

Female Exposure

Pregnancy outcome. The pregnancy outcome of 32 women working in a Swedish hospital laboratory was studied by Strandberg and associates (1978). These authors concluded that there was a slightly increased but significant risk of spontaneous abortion (17 abortions of 71 pregnancies) when the pregnancy was "exposed" to laboratory work (RR=1.7, p=.05). The authors point out that this study was conducted on a relatively small and confounding variables were not controlled.

Baltzar and coworkers (1979) have studied the relationship between delivery outcome and women working in the medical profession. In a study of 1500 women working in hospitals during 1965 - 1975 who gave birth during this period, these authors found that the pregnancy outcome of these women did not differ in a major way from controls. Significant findings were an increase in Cesarian deliveries, an increase in threatened abortions and an increase in perinatal death rate in one year, 1973.

Neonatal health: Congenital malformations. Olsen (1983) studied the frequency of gastrointestinal, limb, and lip and palate malformations in children of female laboratory workers. He found no increased occurrence of these defects among the offspring of lab workers.

A Swedish study by Ericson and coworkers (1984) looked at delivery outcome of 1,161 infants born to laboratory workers and compared them to the total number of births, 98,354, in Sweden in one year, 1976. These authors found an increased number of infant perinatal deaths and congenital malformations. A nested case-control study was designed to study 26 of the cases. No specific type of laboratory or laboratory work was identified more commonly among the cases. Baltzar and coworkers (1979) also found no increase in malformation rates among workers in the medical profession.

Two other Swedish studies have found that laboratory workers are more likely to have infants with congenital malformations of the gastrointestinal tract. Meirik and coworkers (1979) studied perinatal death and malformation rates in 322 deliveries to women working at a Swedish University during their pregnancies. Of these women, 245 were laboratory workers while pregnant. The authors found no effect on perinatal deaths, but there was a significant increase in rate of congenital malformations among laboratory workers. Gastrointestinal defects appeared to be especially elevated. The risk for pregnant women laboratory workers of having a child with gastrointestinal atresia was studied in more detail in a case-control study (Ericson, et al., 1982). This study found that infants with gastrointestinal atresia were more likely than control infants to have a mother who was a laboratory worker.

Oil, Chemical and Atomic Workers

A U.S. survey was conducted of reproductive hazards among male oil, chemical and atomic workers exposed to halogenated hydrocarbons (Savitz et al., 1981). A total of 1280 men from 7 plants responded to a postal questionnaire. Workers in these plants used the chemicals ethylene dichloride, methyl chloride, vinyl chloride monomer, chlordane, epichlorohydrin and perchlorethylene. Oil, chemical and atomic workers not exposed to brominated or chlorinated hydrocarbons served as a comparison group. Subjects were placed, on the basis of occupation, into "higher," "lower" or "no exposure" categories. For the purpose of analysis outcomes were classified as "before hire" and "after hire."

Male Exposure

Infertility. There was a marginally significant increase in infertiltiy reported among highly exposed workers compared with the other levels of exposure. Because the same trend was present both before and after hire, no association between exposure and outcome was put forth. Information on infertility was based on a question inquiring about "trouble getting pregnant." The authors defined infertility as 12 months of unprotected intercourse without conceiving.

Pregnancy outcome of female partner: Spontaneous abortions. For both the high and low categories of exposure an overall increase in fetal loss was revealed, although the difference was not significant when the relative risks for before hire and after hire were compared.

Neonatal health: Congenital malformations. No difference was apparent in the frequency of birth defects found among workers before and after hire. In fact the trend, although not significant was opposite from that which had been hypothesized; i.e., a greater number of children with defects before hire as compared with after hire.

Infant mortality. The most important finding of this industrial study is the increase in infant deaths among the offspring of exposed workers. The rate was 2.3 and 4.6 times as great for the "lower" and "higher" exposure workers, respectively, when compared with nonexposed workers. In their discussion, Savitz and associates (1984) suggested that infant mortality following paternal exposure should be included as an outcome measure in future reproductive studies.

Female Exposure

No relevant data found.

Pulp and Paper Workers

Male Exposure

No relevant data found.

Female Exposure

Neonatal health: Congenital malformations. A cross-sectional study of female employees in the pulp and paper industry in Sweden examined congenital anomalies and perinatal survival from 1973-1977 (Blomquist, et al. 1981). Information on all births was gathered from the Swedish Medical Birth Register. The number of congenital malformations, based on 890 deliveries, was close to the expected outcome. When pregnancies outcomes were divided by specific job categories of the female cohort, the highest frequency of birth defects (4.0%) and perinatal deaths (1.79%) occurred among women in the "converting" section where paper is refined into various products (N.B. these rates are considered low by U.S. standards). The authors noted that some of these workers were exposed to ethylene acetate, glues, and various stains. Laboratory workers also had a high incidence of congenital malformations and perinatal deaths, 3.9% and 1.9%, respectively. This finding is in accord with the results of several other studies on lab workers discussed above. The most common malformations among the lab workers' children were cleft palate and as noted previously for lab workers, atresia of the gut. No job descriptions or exposure levels for any job were included in the study.

Steel Workers

Female Exposure

Pregnancy outcome: Spontaneous abortion. Kolmodin-Hedman et al. (1982) in a cross-sectional study of the steel industry in Sweden examined the rate of spontaneous abortion among female employees. Dividing the factory by work sector, the number of spontaneous abortions was greatest among women employed in the metallurgical and hot milling areas. These were the only two areas where exposure to sulfur dioxide occurs, ranging from 7-25 ppm in metallurgy and 0.5-4 ppm in the hot rolling mills. Other exhaust gases, such as carbon monoxide and nitrous oxide are also produced in these areas. When rates were adjusted for smoking and age, the high frequency of spontaneous abortion was not significant.

Textile Workers

Male Exposure

No relevant data found.

Female Exposure.

Infertility. A case-control study by Rachootin et al. (1983) suggests female exposure to textile dyes is associated with infertility. Using data collected from medical records and questionnaires in Denmark, analysis revealed that women who reported exposure to textile dyes experienced a 5 fold increase in risk of infertility, adjusted for age, education, residence and parity. The risk of infertility among textile workers was greater than for women working with cutting oils, dry cleaning chemicals, lead, cadmium, or mercury. No exposure levels were provided.

Pregnancy outcome: Spontaneous abortion. There are several studies that examine the frequency of spontaneous abortion among women in the textile industry. None of these studies focus on the industry alone; they are generally part of larger, industrial community investigations. Kovoussi (1977) compared the rates of abortion among female industrial textile workers to corresponding rates for women who did not work. The women interviewed in this pilot study were at least 30 years of age, and over 70% of them had been employed in one of two factories in the Iranian community for over 15 years. The study revealed that the textile workers had a significantly higher rate of spontaneous abortion (12%) compared with the nonworking controls. A similar difference was found in the frequency of infant mortality. The author adjusted the rates for age only. There was no discussion or description of the workplace, including possible chemical or physical hazards.

A second investigation of spontaneous abortion among women in textile industries yielded similar findings (Hemminki, K. et al. 1983). However, unlike the study in Iran, this investigation considered the husband's occupation for further analysis. Hemminki and coworkers used the hospital discharge registry to obtain information on the study group and their families in the community of Kokkola, Finland. While women in the town worked mainly in the textile industry, men were employed in the metal, leather and chemical industries. The rate of spontaneous abortion for women in Kokkola was highest among the women in the textile industry (12.2%). This rate differed significantly from women who did not work (6.3%), but not from other economically-active women (11.4%). Specifically, women working as seamstresses in the textile factory had a rate of spontaneous abortion of 20.4%. When the husband's occupation was considered as well, women employed in textiles married to men employed at the metallurgical factory had a rate of spontaneous abortion of 16.0%. The authors suggest that the high rate of spontaneous abortion among the combined occupations may be due in part to the paternal effect. Although the husbands' jobs in the metallurgic factories are unspecified, possible exposures to arsenic, zinc, cobalt, sulfur dioxide, hydrogen sulfide, and cadmium are suggested (see Arsenic).

A final community based study by Hemminki and Niemi (1982) found that women and wives of men employed in rayon textile jobs had an increased rate of spontaneous abortion. The investigators noted that the vicose rayon industries use hydrogen sulfide and carbon disulfide (see Carbon Disulfide). No exposure data was provided.

TRANSPLACENTAL CARCINOGENESIS

Evidence has accumulated over the past 10 to 15 years that prenatal exposure to toxic agents may increase the risk of childhood malignancy. Although in animals there exists substantial evidence of agents which cause transplacental carcinogenesis, there are few documented cases in humans. Perhaps the best understood is that of diethylstilbestrol, which when taken by women during pregnancy to prevent miscarriage, can lead to vaginal cancers in their offspring.

Childhood tumors, in general. Recent epidemiologic research has attempted to link parental exposures before, during, and immediately after pregnancy with the development of childhood tumors. Hemminki and coworkers studied all childhood cancer cases (under age 15) occurring in Finland from 1959 - 1975 and attempted to relate parental occupation to an increased risk of childhood cancers (Hemminki et al., 1981). For maternal exposure, the study found in only one occupational group, women living on farms, a significant increased risk for their offspring to develop cancer. In one subcategory of the food industry, bakers, a significant ratio also existed. With respect to paternal exposure, children of fathers working in motor vehicle driving, farming, and forestry had a significantly elevated cancer risk (Hemminki et al., 1980).

An early study in Quebec related an increased incidence of childhood cancers to the father's occupational exposure to hydrocarbons (Fabia and Thuy, 1974). Fabia and Thuy studied 386 children who died of malignant disease before age 5. They found a significant excess of fathers with hydrocarbon exposure (OR=2.1) among the cases compared with controls. The occupations identified were mechanics, machinists, miners, and painters.

Several studies have attempted without success to confirm this finding. Hakulinen and co-workers (1976) studied 852 cancer cases and an equal number of controls in an attempt to relate childhood malignancies to hydrocarbon exposure. No significant association was seen between newly diagnosed malignancies and hydrocarbon-related occupations.

Kwa and Fine (1980) studied 692 children whose fathers worked in 3 hydrocarbon-related occupations including mechanics and gas station attendants, machinists, miners, lumbermen, painters, cleaners and dyers. These authors found no significant associations between these occupations and childhood malignancies including blood, nervous system, urinary tract, and other tumors, with one exception-- father's occupation as a mechanic or machinist was associated with urinary tract tumors (OR=2.5), but only 9 cases were involved.

Finally, Zack and coworkers (1980) found no association between risk of childhood cancer and parental occupation in the Texas Childhood Cancer Study. The discrepancies between the early study by Fabia and Thuy and the later studies remain inadequately explained. Differences in the use of incidence and mortality data, age ranges for cancer patients, and a host of methodologic considerations have been proposed as possible explanation

CNS tumors. Peters and Preston-Martin (1984; Peters et al., 1981) used the Los Angeles County tumor registry to identify 92 children with brain tumors under 10 years of age. Comparing cases with neighborhood controls matched on sex, race, and age, the study found that at least 3 times as many mothers of children with brain tumors either inhaled chemicals (specific chemicals not given) or were exposed to them on their skin at work. A comparable risk was found in fathers exposed to solvents (specific solvents not given) (RR=2.8). Fathers of cases were also more likely to work in the aircraft industry than fathers of controls.

Childhood nervous system tumors has also been associated with chlordane exposure. Infante and coworkers (1978), in a series of case reports, noted that in 3 of 14 identified cases of neuroblastoma, the pregnant mother had been exposed to the pesticide chlordane either before or during the pregnancy. Two more children were exposed to similar pesticides postnatally.

Wilm's tumor. Controversy also exists about the relationship between Wilms' tumor, one of the more common childhood urinary tract malignancies, and paternal workplace exposure. Kantor and colleagues (1979) used data from the Connecticut Tumor Registry to study 149 children diagnosed with Wilms' tumor from 1935-1973. This group found that there were more than 3 times as many fathers of children with Wilms' tumors in lead-related occupations compared with controls (lead only OR=5; lead and other substances OR=3.7). A less strong association was found between paternal hydrocarbon-related occupation and Wilms' tumor (OR=2.4).

Contrasting evidence comes from a recent study by Wilkins and Sinks (1984) of 62 cases of Wilms' tumor in Ohio. These authors found no significant difference in lead exposure for fathers of children with Wilms' tumors and fathers of population-based controls matched on age, sex, race, and mother's county of residence at child's birth. A significant relationship was found with boron exposure--fathers of cases were more likely to have been exposed to boron (OR=3.5). Differences between this study and the one by Kantor and coworkers included number of subjects studied and design of methodology, among others.

Comments

Evidence that children can get cancers from exposures that were sustained either in utero or before conception by their parents is at present sketchy, but growing. Transplacental carcinogenesis has been shown to occur when mothers lived on farms, were involved as bakers in the food industry, or were exposed to chemicals at work. An increased incidence of childhood cancers were associated with paternal exposures in vehicle driving jobs, farming, forestry, in jobs with solvent exposures, and the aircraft industry. In addition, children of mechanics, machinists, miners, and painters, and those with high lead and boron exposures were shown to have an increased cancer risk.

These studies are notable for their rather interesting discrepancies. There have been several attempts to confirm the increased cancer risks for children of hydrocarbon-exposed fathers, but all subsequent studies have been negative. Similarly, in only one of two studies has paternal lead exposure been associated with development of Wilms' tumor in childhood.

An important problem in studies based on tumor registry data is that chemical exposure is usually drawn from job or occupational titles on birth certificates and this information may provide inaccurate estimates of the true exposure. Exposures as well as outcome should probably be validated with other data sources.

CONCLUSIONS

Given the vast numbers of chemicals used in the workplace, relatively few have been examined as potential reproductive hazards. Of the ones researched, only a small percentage have significant reproductive effects. For many of the chemicals investigated, some studies suggest reproductive toxicity but no other studies may have been conducted or other studies may have disputed the original findings.

Discrepancies between results of studies seem to arise from 4 major factors: 1) differences in levels of exposure of the study groups; 2) differences in accuracy and sensitivity in detecting outcomes; 3) definition of control groups; and 4) whether confounding variables or effect modifiers are controlled:

1) Exposure levels or biological indicators are often not provided. In fact, in some studies, the identity of the chemicals are not revealed, i.e., industry studies.

2) The ability to detect many of the outcomes varies from lab to lab and country to country. For example, some elaborate measures of sperm motility employing video systems may be more sensitive in detecting differences than the older traditional method of watching the sperm under the microscope. Incidence of spontaneous abortions is considerably underreported (some suggest that as high as 50% of pregnancies end in spontan~~eous~~ abortion but only about 15% is reported); however, fewer miscarriages may be missed in countries such as Finland where women, if they are aware of the miscarriage, usually receive treatment.

3) Inadequate control groups are employed; for example, one control

group had higher than normal lead levels (25 mcg/dl); another control group had more chromosomal aberrations than normal. Investigators sometimes compare groups composed of small numbers of participants. This type of errors biases the results towards finding no effects of exposure. Using control groups which are not well-defined or using historical controls drawn from studies of populations with slightly different sociodemographic characteristics may bias the results in an unpredictable direction.

4) More often than not, investigators do not control for important confounders. For example, in studying spontaneous abortions in women at 2 different points in their reproductive histories, before and after employment, it is essential to search and, if necessary, control for differences in parity or maternal age. When looking for differences in birthweight, differences in smoking history should probably be controlled.

One noteworthy observation is that a large percentage of the studies on reproductive hazards are not conducted in the United States (we estimate about 2/3 are conducted elsewhere). By far, most of the epidemiologic studies are conducted in Scandinavia or the Soviet Unon. We propose a number of explanations for this observation. First, in this country it is difficult for researchers to gain access to the workplace; even unions are often threatened by the findings of scientific studies. Second, in the U.S., there exist few large-scale central data bases from which both occupational and reproductive data can be retreived. This is unlike Sweden and Finland where central registries exist and pregnancy data cross-links with occupational history as well as birth certificates, death certificates, and medical records by an individual identification number. In contrast, the registries in the U.S. are essentially restricted to specific birth defects and to tumors. Although a number of states have tumor registries and a few states have birth defect registries, occupation of parents is often not coded. In fact, parent's occupation is not uniformly coded on birth certificates across the country. Many of the outcomes examined are rare events such as birth defects or pregnancy complications. Large numbers are therefore needed to detect differences. The numbers often can only be provided by extraordinarily expensive large-scale studies or by registry data. It is imperative that we improve U.S. data-bases and their accessibility.

In conclusion, although industry has elected to exclude women from jobs which may be hazardous to reproduction, studies demonstrate that workplace exposures are also hazardous to men. Unfortunately, many chemicals which have been studied in men have not been investigated in women and vice versa e.g. DBCP, methylmercury. Future research should examine the reproductive effects of chemicals already found hazardous in the opposite sex. Future research should also focus on early signs of reproductive toxicity, for example, biological or physiologic indicators. Another indicator of subtle changes may lie in the examination of neurodevelopmental outcomes. Behavioral teratologists suggest that low levels of an in utero exposure to a toxic agent may result in only neurobehavioral changes but higher doses of the same chemicals may result in fetal death or in CNS malformations. Yet only for few chemicals have researchers examined the neurodevelopmental effects of in utero exposure.

Appendix: Animal Studies

ANESTHETIC AGENTS --Enflurane/Halothane

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
			Enflurane		
Rat(M,F)	20 ppm 8 hr / day for 63 days (M) for 28 days (F)	inhalation	days 1-21	decr. fetal wt & length (both M&F exposed) decr. M/F sex ratio & incr. letter size (F exposed only) no effect fertility rate, resorption, fetal loss, fetal/placental wt. ratio	Halsey,M.J. et al. 1981
			Halothane		
Mouse (F)	1.0%, 1.5% 3 hrs/days for 3 or 4 days	inhalation	days 1-21	incr. cleft palate, limb hematomas, ossification defects	Smith, B.E., et al. 1971
Rat (F)	10 ppm 4 hrs/wk for 3 wks	inhalation	days 1-21	incr. focal weakening & disruption of nuclear envelope of cortical neurons, abnormal post-synaptic membranes	Chang, L.W. et al. 1974
Rat (F)	Mean conc. 1.35-1.43%	inhalation	days 1-5, 6-10, or 11-15	No effects for rats or rabbits. Mating, fertility and reproductive indices similar to control gp	Kennedy, G.L. et al. 1976
Rat (F)	50,100,200,800, 1600, or 3200 ppm 8 hrs/day	inhalation	days 8-12	no teratogenic effects	Lansdown, A.B.G et al. 1976
	1600 8/hrs day		days 1-21	decr. fetal weight & length no significant incr. in congenital abnormalities	

ANESTHETIC AGENTS--Halothane

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
Rat (F)	10, 250 mg/m^3 r hrs/day, 4.5 days	inhalation	Halothane days 8-13	incr. fetal death	Todorov,S., et al. 1979 abstract
Mouse (F)	0.05%, 30 min or 2 hrs/day, 9 wks prior to mating & 17 days after	inhalation	days 1-17	no effect	Wharton, P.S. et al. 1979
	0.1%, 0.3%, 1.0% 4 hrs/day 9 wks prior to mating & 17 days after	inhalation	days 1-17	incr. incidence of delayed ossification at 0.1% and 0.3% delayed renal pelvic maturation & skeletal variants at 0.3% decr. fertility & incr. growth retardation at 1.0%	
	0.1%, 0.3%, 1.0% 4 hrs/day for 9 days	inhalation	days 6-15	incr. skeletal abnormalities at all levels embryo letrality in 8 of 9 dams; dam 9 all fetuses deformed.	
Rat (M,F)	10 ppm 8 hrs/day for 36 days (M)	inhalation	---	incr. litter size & total no. abnormalities no change fertility, resorption or fetal loss	Halsey, M.J., et al, 1981
	10 ppm 8 hrs/day for 36 days (M)	inhalation		decr. fetal/placental wt. ratio no change fertility, resorption or fetal loss	
	10 ppm 8 hrs/day for 31 days	inhalation	prior to & throughout	incr. M/F sex ratio	

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
		Halothane			
Rat (F)	0.16, 0.32% continuous for 21 days	inhalation	days 1-21	No effect fetal loss, skeletal anomalies, sex ratio	Pope, W.D.B. et al. 1978
	0.32% continuous for 8 days	inhalation	days 1-8	decr. fetal wt. & length incr. developmental retardation	
Mouse (M,F)	0.5% 30 min/day or 2 hr/day .10% 4/hr/day, 9 wks prior to mating and throughout preg. (F)	inhalation	throughout	no effect fertility	Wharton, R.S. et al, 1978
	0.1%, 0.3%, 1.0% 4 hr/day, 9 wks prior to mating and throughout pregnancy (F)	inhalation	throughout	decr. implantation rate, fetal wt. & length at 0.1% decr. implantation rate, no live fetuses at 0.3%	
	3.0% 4 hr/day for 17 wks (M only)	inhalation	throughout	equal reproductive indices	
Rat (M,F)	9 ppm 4hrs/day(F)	inhalation	throughout	decr. mean litter size and no live fetuses gross structural & skeletal defects among offspring	Popovas, 1979
	9 ppm 4 hrs/day 6 or 8	inhalation	--	decr. male fertility	

ANESTHETIC AGENTS--Halothane/Nitrous Oxide

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
			Halothane		
Rat (M)	0.50, 1700 ppm 8 hrs/day for 12 days	inhalation	prior to mating	no changes in fertility, no live offspring, litter size, fetal or placental wt.	Pope, W.D.B. Persaud, T.V.N. 1982
			Nitrous Oxide		
Rat (F)	45-50% N_2O continuous for 2, 4, 6 days	inhalation	day 8	incr. resorption, congenital malformations of vertebrae and ribs decr. fetal wt., survivors, and M/F sex ratio (35M:70F)	Fink, B.R. et al 1967
Rat (F)	15,000 ppm 24 hr/day	inhalation	days 8-13	decr. in no. of pregnancies/ rat incr. fetal death	Corbett, T.H., et al, 1973
	1000 ppm 24 hr/day		days 12-19	decr. in no of pregnancies/ rat incr. fetal death	
	1000, 100 8 hr/day		days 10-13, or 14-19, or 10-19	incr. fetal death at 1000 ppm for diurnal exposure only	
Rat (M)	20% N_2O for 35 days max.	inhalation	--	decr. mature spermatozoa and appearance of multinucleated forms by day 14; recovery of spermatogenesis occurred 3 days post-exposure	Kripke, B.J. et al. 1976
Rat (F)	1.0%, 10%, 50% continuous for 21 days	inhalation	throughout	decr. fetal wt by length incr. developmental retardation. equal gross skeletal anomalies & M/F sex ratio	Pope, W.D.B. et al, 1978

ANESTHETIC AGENTS-Halothane/Halothane & Nitrous Oxide

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
			Nitrous Oxide		
Rat (M,F)	0.5%, 5.0%, 50% 4 hrs/day, 5 days/wk for 5 wks	inhalation	---	no sperm or testical abnormalities, or oocyte destruction	Mazze, R.I. et al. 1983
			Halothane and Nitrous Oxide		
Hamster (F)	0.6% halothane & 60% N_2O 3 hrs/day	inhalation	days 9, 10 or 11	incr. resorption on day 11 only decr. mean fetal wt. and length on days 10 & 11 equal M/F ratio	Bussard, D.A., et al, 1974
Rat (M,F)	1 ppm halothane & 50 ppm N_2O 7 hrs/day, 5 days/wk for 12 wks	inhalation	days 1-15 days 6-15	no significant effects	Coate, W.B., et al 1979
	10 ppm halothane & 500 ppm N_2O 7 hrs/day, 5 days/wk for 12 wks		same	decr. ovulation & implantation efficiency, no major teralogic effects	
	males exposed additional 40 wks after 21 day mating period			cytogenic damage in males to bone marrow & spermatogonal cells at both leves of exposure	
Rat (F)	0.8% halothane 12 hrs (nocturnal or diurnal)	inhalation	Halothane days 6, 7, 8, 9 or 10 or days 6½, 7½, 8½, 9½, or 10½ (single exposure	incr. in vertebral anomalies--days 8 and 9½ incr. in lumbar rib anomalies--days 8,9,10½ incr. resorption diurnal exposure only	Bosford, A.B., Fink, B.R. 1968

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
			Methoxyflurane		
Rat (F)	0.01%, 0.04%, 0.08% continuous for 21 days	inhalation	throughout	no effect gross skeletal anomalies & sex ratio decr. fetal wt & length incr. developmental retardation	Pope, W.D.B., et al. 1978.

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
			Ethylene Oxide		
Mouse(M,F)	50-200 mg/kg 6 hr-30 hr prior to death	i.v.inj.	--	mutagenic effects-incr. in bone marrow cells w/micro-nuclei at 150 mg/kg NB: identical effect in rats at 100 mg/kg	Appelgren, L.E. et al, 1978*
(f)	75 or 150 mg/kg for 3 day periods	i.v. inj.	days 4-6, 6-8, or 8-10	incr. resorptions days 4-6 or 10-12 incr. fetal malformations days 6-8, or 8-10	Kimmel,C.A. Laborde, J.B. 1979*
Rat(M)	1000 ppm for 4 hrs (single dose)	inhalation	--	decr. fertility, no implants per pregnant female incr. mutagenic index during first 5 wks post exposure only	Embree, J.W. et al, 1977
Rat(M,F)	10, 33, 100 ppm 6 hr/day 5 day/wk	inhalation	days 6-15	decr. fertility (F) & fetal body wt at 100 ppm	Snellings, W.M. et al 1982
	same as above	inhalation	days 6-19, gestation & days 5-21 lactation	decr. fertility & litter size, incr.gestation period at 100 ppm	
Guinea pig	49ppm-841 ppm 7 hr/day, 5 day/wk, for 25 wks	inhalation	--	degeneration of testicular tubules & growth depression at 357 ppm. NB. Similar effects not seen in rabbit or monkey. Rats exposed at this dose died within 6 wks, slight testicular toxicity in rats at lower doses.	Hollingsworth, R.L. et al 1956*

*cited by Barlow, S.M., Sullivan, F.M., 1982

CHEMICAL STERLIZING AGENTS-Formaldehyde

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
			Formaldehyde		
Mouse(M)	16-40 mg/kg (single)	i.p.	--	no effects on pregnancy or dominant lethal effects	Epstein, S.S. et al 1972*
Mouse(F)	1% formaldehyde (wiv) & 12-15% methanol at 74, 148, or 185 mg/kg/day	gav.	days 6-15	maternal death at 185 mg/kg, decr. wt gain at 74/mg/kg, no effects implantations, live fetuses, fetal deaths, malformation at other doses	Marks, T.A. 1980*
Rat(F)	0.5 ml of 1 part 40% formaldehyde 3 parts water (2 inj)	s.c.	day 15 or day 18	no effect placental glycogen levels, incr. placental acids & neural lipids	DeAlmeida, P.A.M. 1968*
Dog(F)	0, 125, 375 ppm	s.c.	days 4-56 after mating	no effect on pregnancy rate. litter size, stillbirths, malformations decr. body wt. pups	Hurni, H., Ohder, H. 1973

*cited by Barlow, S.M., Sullivan, F.M., 1982

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
			Arsenic		
Mouse (M)	5 ppm 256 days	p.o. (water)	--	no testicular change	Banko, V. et al 1968*
	50 ppm 256 days	p.o. (water)		degeneration of testicular tissue	
Mouse (F)	10 or 12 mg/kg (single)	inj.	days 7-12	incr. resorption congenital malformations decr. fetal weight	Hood, R.D. 1972*
Mouse (F)	25 mg/kg (single dose)	i.p.	days 6-12	no effect	Hood, R.H. & Bishop, S.C. 1972*
	45 mg/kg (single dose)	i.p.	days 6-12	decr. fetal wt. incr. fetal resorption fetal anomalies including exencephaly, hydrocephaly, body wall, eye and skeletal defects	
Mouse (F)	10 mg/kg 13 days	gov.	day 9-11	incr. congenital malformations (bent tail, open eyelids, cleft palate)	Matsumato, N. Iijima. S.,

*cited by Barlow, S.M., Sullivan, F.M., 1982

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
			Arsenic		
Mouse(F)	40 mg/kg (3 days)	gav.	day 9-11	decr. fetal wt. placental wt. incr. congenital malformations (as above) resorption fetal death	
Mouse (F)	120 mg/kg	oral	days 7-15	maternal toxicity of two dosages was comparable, but i.p. caused comparatively incr. resorption and malformation	Hood, P.D. Thacker, G.T., 1978*
	40 mg/kg	i.p.	days 7-15		
Rat (M,F)	26.8 mg/kg diet 4 wks to 1 yr of age	p.o. (diet)	throughout gestation x 4 litters	no change fertility, fecundity, wt of offspring	Morris, H.P. et al., 1938*
	215 mg/kg diet 4 wks to 1 yr of age	p.o.(diet)	throughout gestation x 4 litters	no change fertility, fecundity wt of offspring	
Rat (F)	20 mg/kg single injection	i.p.	days 7-12	subcutaneous hemorrhage	Beaudoin, A.K. 1974*
	30 mg/kg and 40 mg/kg single injection of one or other	i.p.	days 7-12	decr. fetal wt at all days incr. embryonic death fetal abnormality	
			day 9	resorption, eye defects and exencephaly skeletal abnormalities	
			day 10	resorptions, renal and gonadal agenesis, skeletal abnormalities	
			day 12	skeletal defects only	

*cited by Barlow, S.M., Sullivan, F.M., 1982

METALS--Arsenic

Arsenic

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
	50 mg/kg	i.p.	days 7-12	lethal dose to all embryos	
Rat (F)	30, 30, 50 mg/kg (single)	i.p.	day 9, 10, or 11	decr. fetal wt. incr. resorption, congenital malformation including eye defects, exencephaly, renal agenesis, s.c. hemorrhage, rib and vertebral defects no gonadal agenesis	Burk, D., and Beaudoin, A.R., 1977*
Rat (M)	1 mg/kg	p.o.	--	no dominant lethal effects when mated with control females	Gencik, A. et al., 1977*
Rat (F)	0.0025 mg/kg 7 mo. including pregnancy	p.o. (water)	throughout	incr. post-implantation losses	Nadeenko, V.G. et al., 1978*
Rat (F)	45 mg/kg (single dose either 4 hrs or 24 hrs prior to sacrifice)	i.p.	day 10	4 hrs, no gross anatomical or biochemical effects 24 hrs, incr. neuroanatomical anomalies, failure of placental development decr. yolk sac development in embryo DNA, RNA, and protein synthesis	Fisher, D.L. 1982
Hamster(F)	5 mg/kg	i.v.	day 8	no effect	Ferm, V.H. & Carpenter, S.J.,1968*
Hamster(F)	20 mg/kg	i.v.	day 8	incr. exencephaly resorptions	
	40 mg/kg	i.v.	day 8	death of all embryos in utero	

*cited by Barlow, S.M., Sullivan, F.M., 1982

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
Hamster(F)	20 mg/kg (single dose)	i.v.	day 8	incr. exencephaly, encephalocele, cleft palate, microphalmia and ear malformations	Holmberg, R.E. & Ferm,V.H. 1969*
Hamster(F)	15 mg/kg-25mg/kg single injection	i.v.	day 8	incr.congenital malformations, including anencephaly, renal agenesis, rib malformations, fetal resorption	Ferm,V.H. et al. 1971
Hamster(F)	10 mg/kg with hyperthermia	i.p.	not given	incr.congenital malformations	Ferm,V.H.& Kilham, L. 1977*
Sheep(F)	0.50 mg/kg day for 18-147 days	p.o.	day 1 forward	lambs of normal size and appearance	James, L.F. et al., 1966
	0.75 mg/kg/day for 18-147 days	p.o.	day 1 forward	decr. birth weight	
Boar	poisoning outbreak (dose and length uncertain)	treatment with arsanilic acid	--	decr. semen production libido, sperm motility sperm count, fertility of sperm incr. abnormal sperm morphology	Trace, H. et al, 1974*

*cited by Barlow, S.M., Sullivan, F.M., 1982

SPECIES	LENGTH OF EXPOSURE	EXPOSURE	EXPOSURE	EFFECTS	REFERENCE
			Boron		
Rat (F)	0.4g/kg (2 yr)	gav. or p.o. (water)	--	Mated to control males decr. survival of offspring	Truhaut, R., 1964*
	1.0, 2.0, 3.0, 1 kg (8 mo-12 mo)	p.o. (food)	throughout	decr. litter size, survival of offspring	
Rat (M)	1-5 g/kg (single)	gav.	--	incr. testicular lesions	Bouissou, H, & Castagnol, R. 1965*
Rat (M)	52.5, 175, 525, 1750, 5250 ppm (90 days)	p.o. (diet)	--	decr. test.wt. at 1750ppm test. atrophy at 525, 1750 ppm, no effect at 52.5, 175 ppm	Weir, R.J. & Fisher, R.S. 1972*
	117,350 or 1170 ppm (2 yrs)	p.o. (diet)	--	decr. test.wt., atrophy & shrunken scrotum (1170 ppm) No effects at 117, 350ppm sterility with no spermatozoa (1170 ppm)	
Rat (F)	52.5, 175, 525, 1750, or 5250 ppm (90 days)	p.o. (food)	--	at 1750 (5250) decr. in ovarian wt.	Weir, R.S. & Fisher, R.S. 1972*
Rat (F)	117,350, 1170 ppm (2 yrs)	p.o. (food)	--	at 1170-reduced ovulation, when mated with identically treated males, no litters produced	
Rat (M)	0.08, 0.3, 1.7 mg/kg (6 mo)	p.o. (Water)	--	decr. test. wt. sperm count, motility	Krasouskii, GN. et al, 1976*
Dog (M)	17.5, 175 or 1750 ppm (90 days)	p.o. (food)	--	decr. test. wt. at 175, 1750 ppm. Test. atrophy, degeneration of spermatogenic epithelium at 175, 1750 ppm. No adverse effects at 17.5 ppm	Weir, R.J. & Fisher, R.S. 1972*

*cited by Barlow, S.M., Sullivan, F.M., 1982

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF EXPOSURE	EFFECTS	REFERENCE
			Cadmium		
Mouse (albino) (F)	0.02 mM/kg, single dose	sic.	variable, from 6 to 17th day	placental necrosis and hemorrhage, intra-uterine death of embryo	Chiquoine,A.D. 1965
Mouse(M,F)	10 ppm (6 mo.)	p.o. water	throughout 2 gestations	F_1--incr. number runts post natal deaths F_2--incr. postnatal deaths, stillbirths, congenital malfunctions	Schraeder, H.A. & Mitchener,M, 1971*
Mouse(M)	0.125-1.0 mg/kg	i.p.-1 dose		cadmium evaporated into spermatogenic cells	Lee, L.P. and Dixon, R.L, 1973
Mouse(M)	1 mg/kg	i.p. 1 dose		decr. fertility, recovery in 50-55 days	
Mouse(F)	0.33, 0.63, 2.5 5 mg/kg (single)	s.c.	day 7	On day 18, no cadmium found in fetal tissue, cadmium found in liver, kidney and placental tissue incr. resorption all grps. malformations in 0.63, 2.5, 5.0 mg/kg. abortions in 5.0 mg/kg	Ishizu,S. et al., 1973
Mouse(F)	injection of radio-labelled substance into pregnant mouse	s.c.	day 10	cadmium found in mouse embryo in 1 hr	Walkowski,P.M. 1974*
			day 13	cadmium in embryo, fetus, and placenta at 4th and 24th hr.	

*cited by Barlow, S.M., Sullivan, F.M., 1982

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF EXPOSURE	EFFECTS	REFERENCE
Mouse (M)	1.75 mg/kg (single)	i.p.	--	decr. pregnancy rate	Gilliavod, N.& Leonard,A. 1975*
Mouse(F)	0.25 or 0.5 mg/kg/day (11 days)	s.c.	days 7-18	cadmium found in mouse fetus at low levels	Matsumoto,N, 1975*
Mouse(F)	3 or 6 mg/kg 12 hr before sacrifice	inj.	--	decr. number of oocytes incr. ovarian hemorrhage chromosome anomalies	Shimada, T., et al, 1976*
Mouse(F)	3 and 6 mg/kg (single)	s.c.	--	Ovarian levels at 2.5 & 5ppm 12h after injection	Watanabe, T., et al, 1977*
Mouse(F)	5 mg/kg	i.p.	day 7	incr. resorptions malformations (exencephaly)	Semba, R., et al. 1977
Mouse(F)	3 & 6 mg/kg (single)	s.c.	--	ovarian hemorrhage decr. oocytes with chromosomal anomalies	Watanabe, T., et al. 1977*
Mouse(F)	10, 20, 40ppm	p.o. water	throughout	Fetal growth retardation Anemia. Both prevented by iron supplementation decr. water intake	Webster, W.S. 1978
Rat(M)	0.02 Or 0.04 m-mole/kg single injection	s.c.	--	testicular necrosis (also seen in mouse, rabbit, guinea pig, hamster) atrophy of accessory sex organs	Parizek,J. 1960
Rat (F)	0.04 m-mole/kg (single)	s.c.	--	no effect	
Rat(F)	0.04 m-mole/kg single injection	s.c.	days 17-21	placental necrosis and bleeding. intra-uterine death of embryo	Parizek, J. 1964

*cited by Barlow, S.M., Sullivan, F.M., 1982

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF EXPOSURE	EFFECTS	REFERENCE
Rat(F)	0.02 m-mole/kg	s.c.	last 4 days of pregnancy	death of adult (toxemia-like) placental necrosis fetal destruction	Parizek, J. 1965
Rat(M,F)	10mg/kg (single)	s.c.	1,5,10 or 20 days of age	hemorrhage in brain of young animals	Gabbiani, G. et al., 1967*
Rat (F)	0.02, 0.04 m-mole/kg	s.c.inj	not gestation,given during induced persistent estroces	ovarian hemorrhage (effects prevents by injection of zinc or selanite)	Parizek, J. et al., 1968
Rabbit(M)	0.05 m-mole/kg (single)	s.c.	--	decr.spermatogenesis sperm motility, testes size incr. abnormal sperm morphology, no congenital anomalies in young	Paufler,S.K,& Foote, R.H. 1969
Rat(F)	3 g/day (4 mo.)	inhalation	--	Prolonged estrus cycles incr. length of diestrus decr. wt. gain	Tsuetkova,R.P. 1970
Rat(F)	0.6 ppm 24th day	inhalation	throughout gestation	decr. newborn wt. incr. infant death	Tsvetkova,R.P. 1970
Rat(F)	0.01, 1, 4mg/kg	p.o. water	days 6-14	no effects on implants/dam, live fetuses/dam resorptions, dam or fetal wt. incr. cong. abnormalities at 4 mg/kg esp. genitourinary defects	Nolan, O.A., et al, 1972*

*cited by Barlow, S.M., Sullivan, F.M., 1982

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF EXPOSURE	EFFECTS	REFERENCE
Rat(F)	16 um/kg one injection	s.c.	day 9, 10,or 11	no teratogenic effects	Barr, Jr.M. 1973
Rat(F)	16 um/kg one injection	i.p.	day 9, 10,or 11	congenital malformations including attenuation of abdominal wall and forelimb deformities	
Rat(F)	variable--4-12 mg/kg (4 days)	s.c.	days 13-16	incr. (dose-related) fetal death rate anomalies (micrograthia, cleft palate, club foot, small lungs) decr. fetal wt.	Chernoff, W., 1973
Rat(F)	0.1, 0.4, 1.6 mg/kg	i.v.	day 12, 15 or 20	dose-related transfer to fetus and incr. with advancing gestation. Placental levels high, maternal and fetal level low	Sonawane, B.R. 1975*
Rat(F)	10 ug-10mg/rat	p.o.	day 17	in 24 hr, fetal & maternal blood levels low, placental levels high	Ahokas, et al., 1976
Rat(F)	.016 m-mol/kg (single)	s.c.	day 9, 10, or 11	no teratogenic effect	Vare, A.M., & Monie, I.N., 1976*
Rat(F)	.016 m mol/kg (single)	i.p.	day 9, 10, or 11	decr. fetal wt. incr. resorption cong. abnormalities including anophthalmia, micropthalmia, hydrocephaly, undiscended testes, dysplastic tail	

*cited by Barlow, S.M., Sullivan, F.M., 1982

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF EXPOSURE	EFFECTS	REFERENCE
Rat(M)	0.005 or 0.0005 mg/kg (6 mo)	p.o. (water)	--	decr. sperm count, sperm motility with germinalopithelial damage	Krasouskii,GN et al, 1976*
Rat(M)	0.001, 0.1 mg/l for 30, 60, 90 days	p.o. (drinking water	---	no effect on sominal vesicle or prostate	Dixon, R.L. et al 1976 (abstract)
Rat(M)	100 or 150 mg/kg	p.o.	--	decr. fertility with testicular necrosis	Katsonis, F.N. & Klaassem, C.D., 1977*
Rat(M)	0.001 m mol/kg (1 mo)	i.p.	--	decr.spermatogenesis incr.abnormal sperm atrophy of seminal vesicles	Dwivedi, C. et al, 1977*
Rat(M)	8 or 88 mg/kg diet for 3, 6, 12, 15 mo.	p.o. in food	--	after 3.6 mo.-no effect after 12-15 mo.-spermatogenic tubule damage and interstitial tissue hypertrophy	Senczuk, W., & Zielinska-Psuja, B, 1977*
Rat(M)	25, 50, 100, 150 mg/kg	p.o.	pre-mating	decr. pregnancy among females mated with 100 and 150 mg/kg group, spermatogenesis in males Testicular necrosis	Kotsonis, F.N. & Klaassen,C.D. 1977*
Rat(M)	1 mg, 5 mg (single)	s.c.	--	1 mg-decr. sperm ct. 5 mg-decr. sperm ct, sperm testosterone mating success	Saskema, S.K., et al, 1977*
Rat(F)	3 mg/kg (single)	s.c.	day 15	levels of 1.7ppm in placenta, 0.02 ppm in fetus, 3 days after injection	Ariyoshi, T, et al., 1977*

*cited by Barlow, S.M., Sullivan, F.M., 1982

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF EXPOSURE	EFFECTS	REFERENCE
Rat(F)	0.1, 0.2, 1.1 and 5 ppm	p.o. (water)	throughout	in 0.1 ppm, 0.4 ppm, 1ppm dose cd not detectable in newborns, placental levels 0.4-1.4ppm in 5ppm dose, newborn levels of 0.4-1.2 ppm with placental levels 20 ppm	Pietrzak-Flis, Z., 1978*
Rat(F)	0.1 ppm	inhalation	throughout	fetal liver levels of 0.04 ppm compared with maternal livers levels of 3.3ppm	Prigge, E. 1978*
Rat(F)	2mg/kg (single)	i.p.	day 20	changes in fetabl brain	Rohrer, S.R. et al., 1978*
Rat(F)	10 or 25 ppm	p.o. water	throughout gestation	incr. fetal bone calcium decr. fetal kidney and liver calcium	Kahman, B.J. et al., 1978*
Rat(F)	0.04, 0.08, 0.12 ppm 24th/day	inhalation	throughout gestation	dose related reduction in maternal wt. gain	Prigge, E. 1978*
Rat(F)	0,10, 25ppm	p.o. water	day 0-21	incr. fetal bone calcium decr. liver and kidney calcium	Walter & Kelman, 1978 (abstract)
Rat(F)	8.6 or 17.2 ppm	p.o. (diet)	throughout pregnancy	decr. neonate iron levels neonate hematocrit	Choudbury,H, et al, 1979*
Rat(F)	10mg/kg (3 weeks)	p.o.	--	decr. pregnancy	Sutou S., et al 1980*
	0.1 or 1mg/kg (3 weeks)	p.o.	--	no fertility effect	
Hamster(F)	2mg/kg (single)	i.v.	day 8	decr. number embryos incr. embryo resorption exencephaly micropthalmus, cleft lip and palate	Ferm,V.H. 1969

*cited by Barlow, S.M., Sullivan, F.M., 1982

METALS--Cadmium/Lead

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF EXPOSURE	EFFECTS	REFERENCE
Hamster(M)	1 mg(single)	s.c.		in 1 mg dose decr. test wt serum testosterone	Lau, I.F. et al., 1978
			Lead		
Mouse(M,F)	1% lead acetate in food for 2 wks	p.o.(diet)	--	incr. chromosome aberrations in leukocytes	Muro, L.A., & Goyer, R.A. 1969
Mouse(M)	1.64 gram over 25 days	p.o. water	--	no effects on pregnancy rate, embryo death decr. total implants incr. mutageniety at 3.6 wks, part-exp.	Varma, M.M. 1974
Rat(F)	64 mg/kg diet	p.o. (diet)	throughout	maternal transfer of lead to fetus, incr. lead content of newborns x 8	Morris, H.P. et al, 1938
Rat(F)	512 mg/kg diet	p.o. (diet)	throughout	maternal transfer of lead to fetus, incr. lead content of newborns x 40	
Rat(M,F)	64 mg/kg diet 4 wks to 1 yr of age	p.o. (diet)	throughout gestation x 4 litters	no change fertility, fecundity, wt of offspring decr. femur wt.	Morris, et al. 1938
	512 mg/kg diet 4 wks to 1 yr of age	p.o. (diet)	throughout gestation x 4 litters	no change fertility, fecundity, wt of offspring incr. kidney wt. decr. liver size, growth femur wt.	

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
Rat (F,M)	10% lead as lead acetate	p.o. (food)	throughout	On F_1 lead-toxic rats mated: Toxic fem. with control male. decr. litter size pup birth wt., pup survival Tox. male with control female decr. litter size, pup birth wt, pup survival Mating- toxic male and female results in cumulative decr. litter size, pup birth wt., pup survival.	Stowe, H.D.& Goyer, R.A. 197'
Rat(M,F)	5 mcg or 100mcg for 30 days	p.o.	--	male, incr. wt of prostate, hyperplasia, female, 5mcg group--irregular estrus cycle, 100 mcg group--persist. vag. estrus with no corpora lutea	Hilderbrand, D.C et al, 1973
Rat(F)	25-79 mg/kg	i.v.	days 8-17	incr. malformations including urorectocaudal syndrome on day 9 toxicity but not teratogeniety on days 10-15 hydrocephalus &CNS defect on day 16, lead passed into fetus, placenta limited transfer	McClain, R.M. & Becker, B.A. 1975
Rat(F)	5 or 25 mg/kg (1 dose)	i.v.	day 17	5 mg and 25 mg decr. mat. wt. gain, birth wt. 25 mg. incr. gest. length pup death, anomalies	Minsker, D.H. et al., 1982
Rat(F)	5 or 25 mg/kg /day (21 days)	p.o.	days 1-21 post-partum	no effect on survival, wt. gain, anomalies	Minsker, D.H. 1982

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
Rat(F)	0.5, 5, 50, 250 ppm	p.o. water	Weaning through mating, gestation, & lactation	Delayed vaginal opening Normal estrus cycles, pregnancy rates, litter no. decr. wt, at weaning with delayed phys. & behavioral devopment	Kimmel, G.A. et al,
Chick embryos	0.05 to 10.0 mg/eg (1 dose)	inj into egg	day 2,3,4, 7,8,9,10, 12 or 15	day 2, incr. fetal death day 3,4 incr. fetal death brain hemorrhage, neusanatomy defects day 7, incr. fetal death total brain injury day x-15, larger doses req. for brain injury and fetal death	Karmofsky, D.A. 1952
Chick embryo	0.005-0.080 mg/egg	inj.into egg	day 2 of incubation	incr. cardiac lesions, aortic stenosis valve defect thin ventric. walls	Gilani, S.H. 1973
Chick embryo	0.005-0.080 mg/egg	inj.into egg	day 8 of incubation	Abnormalities included reduced body size, limb, neck, beak, abn. microphth almid.	Gilani,S.H. 1973
Chicken(F)	1% lead acetate from age 4 wks	p.o.(food)	--	incr. incidence abn.egg shells, lead conc. in yolk, incidence of digit curvature in offspring	Stone, H.D. et al,
Hamster(F)	50 mg/kg (1 dose)	i.v.	day 8	decr. no embryos. incr. embryo resportion tail defects	Ferm, U.H. 1969

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
Sheep(F)	5 mg/kg/day for 45 days, 9 mg/kg/day for 59 days, 9 mg/kg/day for 106 days, 5 mg/kg/day for 106 days	p.o.	days 1-45 days 1-59 days 1-106 days 1-106	5 mg/kg/day for 45 or 106 days no effect on abortion rate; 9 mg/kg for 59 or 106 days incr. abortion rate	James, L.F., et al, 1966
Monkey(F)	10 mg/1wk for 4 wks, then 20mg/wk for 7 mos.	i.v.	--	decr.no. of menstrual cycles, sex, skin color, hemocrit/hemoglobin ovaries were flat and white showing degeneration of follicles	Vermande-VanEck, G.J., & Meigs, J.W., 1960.
			Mercury		
Mouse(F)	0.1 mg/day (8 days, 0.2 mg/day (12 days)	s.c.	--	decr. no. of estrus cycles	Lach, H. & Ireto, Z, 1972*
Rat(F)	0.02, 0.04 m-mole/kg	s.c.inj	given during persistent estrous	pale ovaries	Pariack, J., et al, 1968
Rat(F)	.3ppm for 6/h day(21 days)	inhalation	--	incr.length of estrus cycles	Baranski, B.,& Szymczyk,I, 1973*
	.3 ppm for bh/day	inhalation	3 wks pre-pregnancy & on days 7-20	decr. live litter size	

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
Hamster(F)	2,3,or 4 mg/kg (single)	i.v.	day 8	dose-related incr. in resorption, growth retardation, cong. malf. including exencephaly, encephalocele, anopathalmia, microph thalmia, cleft lip & palate, rib fusions, syndactgly	Gale, T.F. & Ferm, U.H. 1971*
			Methylmercury		
Mouse(F)	0.16 mg/20g	inj.	day 7 or 9	no obvious abnormalities at birth, decr. at weaning, survival to weaning, altered behavior (latency, defecation, urination, barking) nurolog. impairment	Spyker, J.M. et al, 1972
Mouse(F)	Methylmecuric chloride at 30 mg/kg (single)	p.o.	day 6-13	incr. cleft palate micronatia, muroglasica, brain defect	Inouye, M., et al, as cited by Wilson, & Fraser F.C.,(eds), 1977
Mouse(F)	methylmecuric chloride 0.1-2.0 mg/kg	p.o.	day 10	at 0.5 mg/kg and above, incr. fetal death	Kawabe, H., 1972 as cited by Wilson, J.G. &Fraser, F.C. (eds) 1977
Mouse(M)	1mg/kg (single) dose precedes mating by 7 days	i.p.	--	decr. fertility early stages of spumatogenesis	Lee,I.P. &Dixon, R.L. 1975 as cited by Nisbet, I.C.T.,& Kareh, N.J. 1983

*cited by Barlow, S.M., Sullivan, F.M., 1982

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
Mouse(F)	4 or 8 mg/kg (single)	i.p.	day 10	incr. fetal death, resorp., cong. anomal. incl. cleft palate, anophthalmia, micrognathia, exencephaly, missing limbs, facial deformities	Su, M., & Okita, G.T., 1976, as cited by Nesbit, I.C.T. & Larecj N.J. 1983
Rat(F)	dimethylmucric sulfide 0.1mg/kg	p.o.	throughout	decr. fetal wt. incr. enonatal death, effects on post natal development	Fujita, E., 1969, as reported by Wilson, J.G. & Fraser,F.C,(eds) 1977
Rat(F)	Methylmucuric chloride 1.4 mg/kg	p.o.	days 0-20	brain cell changes	Nanaka, I, 1969 as reported by Wilson, J.G. & Fraser, F.C.(eds) 1977
Rat(F)	methylmercuric chloride 6or 8 mg/kg	p.o.	days 7-20	decr. birth wt. litter size	Courtney,K.D. 1971 as citedby Wilson, J.G, & Fraser,F.C.(eds) 1977
Rat(F)	Methylmercuric chloride 5mg/kg	p.o.	days 0-12	incr.fetal death, brain defects, hemorrhage and edema	Murakami, U. 1972 as cited by Wilson, J.G., &Fraser, F.C. (eds) 1977

*cited by Barlow, S.M., Sullivan, F.M., 1982

METALS--Methylmercury

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
Rat (F)	10 uCi ^{203}Hg	s.c.	day 16, 18 or 20	Placental transfer, milk transfer, conc in fetal kidney	Mansour, M.M. 1973
Rat (F)	25 ppm continuous	p.o.water	days 1-20	decr. size of liver and kidney of fetus	Chen, W.J. et al (1979) (Abstract)
Hamster (F)	methylmercuric chloride, 8mg/kg	i.p.	day 5,8 or9	incr. fat resporp. cong. anom. including club foot, hydrocephalus	Harris,S.B. et al, 1972 as cited by Nisbet, I.C.J. & Karch, N.J. 1983
	4mg/kg	i.p.	day 8	none	
	2 or 4 mg/kg/day	i.p.	days 1-14	at 2 mg/kg, fetal resorp. cong. malf. incl. hydrocephalus, clubfoot, cleft palate, microgrulhia	

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
			Carbaryl		
Mouse(F)	100 or 150mg/kg/ day (9 days)	gav.	days 6-9	No effect on fet. wt., length, in preg., fetus litter resorption.	Murray, F.J., et al, 1979
Mouse(F)	1166mg/kg 1 day (9 days)	diet	days 6-15	decr. fetal wt. & length	
Mouse(M)	200,400,or 800 mg/kg/day (5 days)	i.p.	--	no effect on test. wt., sperm ct., % abn. sperm	Ostolloh, J. et al., 1983
Rat(M,F)	3, 7, 25, 100, or 200 mg/kg from age 5 wks to lifetime	p.o.	throughout	no effect on fertility gestation, ui ability, lactation or no. of pups at weaning	Weil,C.S., et al, 1972
Rat(F)	20, 100, or 500 mg/kg/day for 21 days, 7 days, 10 days	p.o.	days 1-21 days 1-7 days 5-15	no effect on fertility, gest., fet. wt., gross anomalies, at 500, decr. maternal wt gain.	
Chick embryo	1.0, 2.5, 5.0 & 10.0 mg (5 or 12 days)	inj. into embryo	prior to incubation	5 days, incr. mort at 2.5 5.0 and 10.0 mg no effect on exter. abn. 12 days, incr. mortality at 2.5, 5.5, 10.0 mg abnormalities inc. cleft foot, ophthalmea	Savarty, W.J. 1981
Rabbit(F)	150 or 200 mg/kg day (12 days)	gav.	days 6-18	decr. fetal wt. at 150 mat. wt. gain, skel. ossific at 200 incr. omphalocele at 200	Murray,F.J. et al, 1979

*cited by Barlow, S.M., Sullivan, F.M., 1982

PESTICIDES--DBCP

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
			DBCP		
Mouse(M)	75, 150, or 300 mg/kg/day for 5 days	i.p.	--	No effect on testes wt., sperm ct., %abn. sperm	Osterloh, J. et al, 1983
Rat(F)	12.5, 25.0, 50.0 mg/kg, day for 9 days	not stated	6-15 days	no teratogenic effects, no DBCP in fetal tissue decr. fetal wt., with incr. dose	Ruddick, J.A. & Newsome, W.H., 1959
Rat(M)	5 ppm for 7h (50 doses)	inhalation	--	test. atrophy, degen.change decr. spermatogenesis, and incr. abn. sperm	Tocbelsan, T.R. et al, 1961
Rat(M)	0.05, 0.5, 5mg/kg/day (10 wks)	p.o.	males mate with control females	in 5 mg group, no preg. occurred, in 0.5mg group, decr. no preg., in 0.05 mg group, no effects seen	Rakhmatullaev, N. N., 1971*
Rat(F)	5mg/kg/day (10 wks)	p.o.	mated with control males	decr. fertility	
Rat(M)	100mg/kg (single)	p.o.	--	single dose, decr. no. of spermatogonia, sperm count, sperm motility	Reznik, R.B. & Sprinchan, G.K 1975*
	10mg/kg/day (4-5 mos)		--	chronic dose decr. sperm count, sperm motility	
Rat(F)	100 mg/kg (single)	p.o.	--	single dose incr. in estrus cycle	
	10 mg/kg/day (4-5mos)		--	chronic dose prolonged cycles with cessation developing	

*cited by Barlow, S.M., Sullivan, F.M., 1982

PESTICIDES--DBCP/DDT

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
Rat(M)	10ppm (14 wks)	inhalation	mated with control females	incr. post-implant deaths	Rao, K.S., et al, 1979*
Rat(F)	12.5, 25, 50 mg/kg/day (9 days)	gav.	days 6-15	in 25 and 50 mg groups, decr. maternal wt.gain No effect on implants/dam or malformations 50 mg group fetal wt reduced	Ruddick, J.A. & Newsome, W.H. 1979*
Rabbit(M)	10ppm(8wks)	inhalation	--	testicularatrophy	Rao, K.S., et al, 1979*
			DDT		
Mouse(M,F)	7ppm for 30 days pre-mating and 7 ppm for add'l 90 days	p.o.(food)	throughout	incr. litter size decr. fertility	Ware, G.W.,& Groc , E.E. 1967
Mouse(F)	2.5mg/kg (single)	p.o.	1st,2nd,or 3rd. trimester	2nd & 3rd trimester-depressed acquisition of conditioned avoidance response in offspring	Al-Hachim, G. & Fink, G.B. 1968
Mouse(M,F)	2.0, 20, 250,ppm for life at weaning	p.o. (food)	throughout	decr. lifespan in 1st generation at 250ppm	Terracini, B. et al, 1973
Mouse(M)	12.5,25 or 50 mg/day(10 days)	gast.intub.	--	no effect on testes wt. sem.vesicle wt., prostate fructase conc. at 25 & 50mg, decr. testast. conc. in ant. prost. liver metab. of testost.	Lloyd, J.W., et al, 1974

*cited by Barlow, S.M, Sullivan, F.M. 1982

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
Mouse(F)	50 mg/kg/wk for 4 wks	inj.	injection administered day of delivery	decr. in fertility in offspring	Kihlstrom, J.F. et al, 1975
Rat(M,F)	200,400, 600 or 800 ppm (life)	p.o.(food)	--	F. fibroma and cellular proliferation of various	Fitzhugh, D.G. & Nelson,A.A. 1946
Rat(F)	140 mg/kg/day (3 days)	i.p.	--	accumulation in uterus & oviducts, incr. in oviduct-wt & glycogen content (effect also found in quail and children)	Bitman, J. et al, 1968
Rat(M,F)	20 or 200 ppm starting at 21st day of life, through 2 generations	p.o. (food)	throughout	decr.fertility in F. generation, survival of young at 200 ppm. Incr. fertility in 3rd breeding of F, fertility in aging females No change in sex ratio, teretogeniety, litter size, birth rate, wt. at weaning	Ottoboni, A. 1969
Rat(F)	200 ppm beginning at 21 days daily for 2 years	p.o. (food)	throughout	incr. successful breeding after normal age of menopause	Ottoboni, A. 1972
Rat(F)	75, 150ppm 8 and 36 weeks	p.o. (diet)	not pregnant	at 50 ppm, after 36 weeks decr.fertility (absence of reproductive success) incr. ovarian follicular cysts.	Jonsson, H.T., et al, 1976

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
Rabbit (F)	50 mg/kg/day (3 days)	p.o.	days 7,8,9	incr. premature litters resorption decr. fetal birthrate no effect on malformation	Hart, M.M., et al, 1971
Dog	1.0, 5.0, 10.0 mg/kg/day for life starting at weaning	p.o. (food)	throughout	no effect on gest. length, fertility (MSF), implantation, pup viability, litter size, sex ratio, or gross survival, 2nd generation, decr. reduction in age at puberty	Ottoboni, A. et al, 1977
			Dioxin		
Mouse (F)	3 mcg/kg/day (9 days)	s.c.	days 6-15	no effect on no. litters fetal mort., fetal wt., mat. wt. gain, no. live litters, no fetuses/litter, incidence congenital anomalies (These results also found in rat)	Courtney, K.D. and Moore, J.A. 1971
Mouse (M)	40 mg/kg, 2,4-D and 1, 4,5-T &, 2.4 mg/kg or 0.16 mg/kg TCDD; or 20 mg/kg 2,4-D and 2,4,5-T and, 0.16 mg/kg or 1.2 ug/kg TCDD (daily)	p.o. diet	throughout	equal implants, resorptions, live fetuses no incr. congenital malformations, no effect, post natal growth.	Lamb, J.C. et al, 1981

PESTICIDES--2,4,5-T and EDB

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
Rat(F)	0.125 or 2.0 or 0.5 mcg/kg/day (2 wks)	gav.	pre-mating	0.5. decr. maternal wt. gain, incr. post-implantation loss 2.0 decr. ovulation, mat. wt gain, incr. pre & post-imple. loss; fetal growth retard, cong. half inc. cystic kidney, gastro int. hemorrhage	Giavini, E. et al, 1982
Rabbit(F)	0.1, 0.25, 0.5, 1 mcg/kg/day (9 days)	p.o.	days 6-15	0.25, 0.5 decr. mat. wt. gain incr. fetal anomalies inc. kidney and skeletal post-implant. losses 1.0 decr. mat. wt. gain no implants incr. postimplant losses	Giavini, E. et al, 1982b.
Mouse(F)	50, 100 or 125 mg/kg/day (9 days)	s.c.	2,4,5-T days 6-15	decr. fet. wt. at 100, 125 maternal wt. gain at loo	Courtney, K.D. & Moore, J.A. 1971
Rat(F)	10, 21.5, 46.4, 80.0 mg/kg/day (9 days)	s.c.	days6-15	decr. maternal wt. gain at 46.4 mg/kg No effect on no. litters, fetal mort. fetal wt., no live litters, no live fetus/litter, incid. cong. anomalie	Courtney, K. D. & Moore, J.A., 1971
			EDB		
Mouse(M)	18 mg/kg	i.p.	mated with control females	no effects on pregnancy or dominant lethal effects	Epstein, S.S., et al, 1972
	90 mg/kg	i.p.	mated with control females	no effects on pregnancy or dominant lethal effects	

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
Mouse (F)	20,38,80 ppm for 23 hr/day	inhalation	days 6-16	decr. food consumption at all doses. decr. maternal wt loss & fetal wt. at 30 & 80 ppm	Short, R.D. et al, 1978
Rat(F)	20, 30, 80 ppm 23 hr/day	inhalation	days 6-16	decr. food consumption at all doses decr. maternal wt. loss & fetal wt. at 30 & 80 ppm incr.resorption and fetal mortality at 80 ppm	Short, R.D. et al, 1978
Rat(M,F)	Male 19, 39, 89 ppm 7hrs/day, 5 day/wk for 10wks	inhalation		Male: 89ppm decr.testicular wts. and reduced serum testosterone conc. decr. fertility atrophy of testes, prostate, seminal vesicles	Short, R.D. et al, 1979
	Female 20, 39, 80 ppm 7 hrs/day 7 days/wk for 3 wks	inhalation	exposure before pregnancy	Female: 80 ppm incr. mortality & morbidity abnormal estrus cycle normal liters produced after termination of exposure	
Chicken (F)	5-7.5ppm	p.o. food	--	decr.egg size impaired ovarian functions	Alumot, E.& Mandel,E. 1969*
	90 ppm		--	cessation of egg laying	
Bull(M)	4mcg/kg every other day for 12 or 21 days	p.o.	--	incr. sperm morph abn.	Amir, D., 1973

*cited by Barlow, S.M., Sullivan, F.M., 1982

PESTICIDES -- Epichlorohydrin

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
Epichlorohydrin					
Mouse(M)	150 mg/kg	i.p.	prior to mating w/unexposed F	no effect pregnancy rate, early fetal death, implantations	Epstein, S.S. 1972*
Rat(M)	15mg/kg for 12 days	p.o.	--	decr. fertility w/in reversible effect, no histoligical charges	Hahn, J.D. 1970
Rat(M)	100mg/kg (single dose) over 20 wks	p.o.	--	decr. size of spermatocoeles, & fertility at 8 wks, large retention cysts in testes led to sterility by 12 wks	Cooper, E.R.A. et al, 1974*
Rat(M,F)	5, 25, 50ppm 6hr/day, 5 day/wk for 10 wks	inhalation	prior to mating	decr. fertility (M)if mated during exposure w/ rapid recovery (50ppm) decr. implantations at 25 and 50 ppm, no effects female	John, J.A. et al
Rat(M)	100 ppm 7hrs/day, 5 days/wk for 12 days	inhalation	--	normal sperm content with incr. no. of nucleated cells no epididymal or testicular changes	Manufacturing Chemists Association 1979*
Rabbit(M)	5,25,50ppm 6h/day, 5 days/wk for 10 10 wks	inhalation	prior to mating	no effect fertility, testicular function, sperm motility, viability, morphology	John, J.A. et al

*cited by Barlow, S.M., Sullivan, F.M., 1982

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
Hexachlorobenzene					
Rat(M,F)	10-640ppm	p.o. (food)	pre-mating & throughout	decr. litter size, post-natal survival at 80-160 ppm with wt. at 80ppm 40 ppm--no effect	Somers, E.,etal reported by Courtney,K.D. 1979
Monkey(F)	8-128mg/kg (60 days)	p.o.	--	Ovarian change at 8 and 32 mg/kg; greater at higher doses	Latropoulos, M.J. et al, 1976 cited by Courtney,K.D. 1979
Kepone					
Mouse(F)	2.0, 4.0,8.0, 12.0 mg/kg/day for 9 days	gast. intub.	days 7-16	incr.fetal mortality at 12 mg.	Chernoff, N, & Rogers,E.H. 1976
Rat(F)	1.0, 2.0, or 4.0 mg/kg/day for 20 days	gast. intub.	day 2-21	at 2.0, only 1/3 healthy pups, 2.0, all abortions and stillbirths	Rosenstein, L. et al (abs.)
Rat(D)	2.0, 6.0, 10.0 mg/kg/day for 9 days	gast. intub.	day7-16	decr. maternal wt. gain at 2, 6, 10 fetal wt. at 6, 10; ossification at 6, 10; incr. anomalies of kidney, testes, brain	Chernoff,N. &Rogers, E.H. 1976
Rat(F)	15 mg/kg body wt daily	gav.	days 14-20	persistent vaginal estrus, anovulation, tonic levels of serum estradiol.	Gellert, R.J. Wilson, C. 1978

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
Rat(M,F)	30 ppm	p.o.(food)	--	Male incr. liver wt. testosterone levels decr. litter size when mated Female incr. liver wt. uterine wt. decr. ovaries wt., estradiol, LH level, constant estrus.	Hammond, B. et al, (abs) 1978
Rat(F,M)	15 mg/kg	gav.	days 14-20	Female 12 of 20 developed persistent vaginal estrus	Gellert, R.J. &Wilson, C. 1979 (abstract)
Quail(M)	200 ppm/day for 42 days	p.o.	--	Test. enlargement & atrophy decr. fertility	Eroschenko, U.P. 1978

POLYBROMINATED BIPHENLYL/POLYCHLORINATED BIPHENHL --PBB

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
			PBB		
Mouse (F)	50,100,1000ppm	p.o.(diet)	days 7-18	incr. placental transfer of 0.53 ppm PBB in exposed fetuses vs. 0.05 ppm in controls and incr. maternal liver wt. at 1000 ppm decr. fetal wt. at 1000 ppm, no differences in congenital abnormalities as compared with controls	Corbett,T.H. et al 1975*
Mouse(F)	0,100,200 ppm	p.o.(diet)	days 4-16	incr. no resorbed fetuses, at 200 ppm only	Preache, et al, 1976*
	0,100,200 ppm	p.o.(diet)	days 8-16	decr. fetal body wt. at 200 ppm only	
	0,50,100ppm	p.o.(diet)	days 8-16 pregnancy	decr. litter size at 100 ppm	
	0,50,100ppm	p.o.(diet)	days 1-29 lactation	incr. pup mortality decr. fetal body wt & locomotor activity at 100 ppm only	
Mouse(M,F)	0,50,500 mg/kg (single dose)	gav.	--	no effect chromosome or chromatid breaks. incr. in gaps at 24 and 48 hr both doses	Wertz, G.F., Fiscor,G. 1978*
Rat(F)	0,100,1000ppm	p.o.(diet)	days 7-20	decr. fetal wt. (dose response seen) no effect implants, resorphons, malformations in any group.	Corbett, T.H. et al, 1975

*cited by Barlow, S.M., Sullivan, F.M., 1982

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
			PBB		
Rat (F)	40, 200, 400, or 800 mg/kg (single dose)	gav.	day 6, 7, 8, 9,10,11or 12	incr. resorption rates days 6-10, at 400 or 800 mg/kg (cleft palate & hernia) days 7-12 at 400 or 800 mg/kg incr. placental transfer, day 12 at 800mg/kg. decr. fetal/placental wts at 400 or 800 mg/kg	Beaudoin, A.R. 1977*
Rat (F)	0.25, 0.5, 1.0, 5.0, or 10.0 mg/day	gav.	days 7-15	decr. maternal wt gain at 0.25 mg incr. maternal liver wt. 1.0 & 5.0 mg, no effect on no. of implants, live fetuses, resporphon, or fetal wt.	Harris,S.J., et al, 1978*
	0 or 10 mg	gav.	days 7-15	decr. in pup wt. from 3 days to 60 days after birth; M pups more affected than F. incr. in post natal mortality	
Rat (M)	0,50,100,150 200 ppm	p.o. (diet)	--	incr. liver wt. all levels wt of testes & seminal vesicles not affected	Harris, S.J. et al, 1978*
Rat (F)	50ppm	p.o. (diet)	days 8-21	incr. placental transfer	Rickert, D.E. et al 1978*
	50 ppm	p.o. (diet0	days 8 gestation through day 14 lactation, or days 1-14 lactation only	incr. liver & G.I. PBB concentration found in pups	

*cited by Barlow, S.M., Sullivan, F.M. 1982

PBB /PCB--PBB

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
Rat (F)	100 mg/kg every other day	gav.	days 6-16	no effect on implants, resorption or fetal wt., or congenital malformations	Wertz, Ficsor, 1970*
Rhesus Monkey (F)	0.3 ppm for 7 mo.	p.o. (diet)	--	incr. wt. loss during exposure incr. length menstrual cycle after 6 mos. decr. progesterone levels poor pregnancy outcome; fetal death, low birth wt., postnatal wt. gain	Allen et al. 1978*
Bull (M)	unspecified	p.o. (diet)	--	reduced or absent spermatozoa & few spermatogenic cells	Cook, H. et al., 1978*
Heifer	0, 0.25, 250 or 25,000 mg/day for 60 days	p.o.	throughout	abortion & fetal death in 6/6 fetuses, 25,000 mg/kg no effects of toxicity lower doses	Durst, H.I. et al., 1978*
			PCB		
Mouse (F)	0.025 mg/day for 10 wk (clophen A60)	oral intubation	--	incr. length of estrus cycle, decr. fertility	Orberg, J., Kihlstrom J.F. 1972
Mouse (F)	50/mg/kg/wk for 4 wks	inj.	inj. administered day of delivery	decr. fertility in offspring	Kihlstrom, J.F. et al, 1975
Mouse (M)	50, 200 ppm for 2 wks	p.o.	--	no effect, male organ wts. decr. (13%) sperm conc./mg. of testis at 200 ppm incr. liver wt at 50 ppm	Sanders, O.T., et al. 1977

*cited by Barlow, S.M., Sullivan, F.M., 1982

PBB /PCB--PCB

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
			PCB		
Mouse(F)	0.94, 8.4, or 8.6 ppm (Kanechlor-500)	p.o. (diet)	days 1-18	placental transfer 0.1-0.2% of total maternal intake for all doses	Masuda, Y, et al, 1978*
			throughout pregnancy, lactation	incr. transfer of PCBs in mil of 1-5 wk old offspring	
Rat(F)	10,50 mg/kg/day (Arochlor1254)	p.o.	days 7-15	no effects in live litter size at birth, stillbirths, litter wt., or survival to weaning	Curley, A, et al, 1973*
Rat(F)	75, 150 ppm 8 and 36 weeks (Arochlor)	p.o. (diet)	--	at 150ppm, after 36 wks: decr. conc. plasma progesterone decr. fertility (absence of reproductive success) changes in ovarian stromal cells	Jonsson, H.T., et al, 1976
Rat(M)	30 mg/kg (Arochlor)	gav.	days14-16	incr. testicular wt.	Gellert, R.J., Wilson, C. 1979 (abstract)
Rat(F)	0, 5, 500 ppm to adults daily	p.o. diet to adults lactation by pups	throughout	decr. litter 500 ppm decr. body wt at 50 & 500 ppm; effect on thyroid glands of pups	Lamb, J.C. et al,1981 (abstract)
Rat(F)	8, 32, 64 mg/kg (Aróchlor)	oral intubation	day of delivery lactation	offspring:exposed male, decr. fertility in male and female; decr. litter size; incr. resorption rate decr. wt ventral prostate and seminal vesicle enlarged in male testes	Sager, D.B. 1981

*cited by Barlow, S.M., Sullivan, F.M., 1982

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
Rabbit(F)	1, 10, 12.5, 50/mg/kg/day (Aroclor 1254)	p.o.	throughout	no effect 1 or 10 mg/kg decr. maternal wt gain high incidence abortion, resorption, fetal death	Villeneuve, E. et al (1971)*
Pig(F)	1, 10, 20, 30 mg/kg/day (Aroclor 1242)	p.o.	throughout pregnancy & lactation	incr. fetal death decr. no. of live births. litter no effect body wt. or postnatal mortality	Hansen, L.G. et al 1975*
Dog(F)	0.25, 1.0, 5.0 mg/kg/day (Arochlor 1254)	p.o.	throughout pregnancy & lactation	at 5 mg/kg only: decr. no of pregnancies mean litter size incr. resorption & postnatal deaths, some congenital malformations	Earl, F. L., et al (1974)*
Rhesus Monkey(F)	2.5, 5.0 ppm for 1.5 yrs (Aroclor 1248)	p.o. (diet) (adults) lactation (infants)	before and during	PCB in tissues of infants at births; after 2 mo. infants had facial acne, edema, swelling eyelids, loss of facial hair. 3 of 6 infants expired 8 mo. after birth, 3 survivors showed improvement after weaning	Allen, J.R., Barsotti, D.A. 1976

*cited by Barlow, S.M., Sullivan, F.M., 1982

SOLVENTS --Benzene

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
			Benzene		
Mouse(F)	10-15 days before mating	ovaries painted with benzene	pre-mating	decr. number of litters incr. abnormal cleavage of blastocyst with death hemorrhages, congenital abnormalities, inc. tail defects, pre-weaning mortality	Batra, B.K., 1966* Solomon, N.S,& Batra, B.K, 1964* Sridharan, B.N., Batra, B.K., et al, 1963*
Mouse(F)	3 ml/kg (single)	s.c.	one of days 11-15	incr. congenital malformation, inc. cleft palate, agnatina and micrognatia	Watanabe,G. & Yoshida, S. 1970*
Mouse(F) and Offspring	prenatal exp. 4 ml/kg postnatal exp. 1 ml/kg/day inj. at 10 wks (5 doses)	inj. inj.	day 9 or 12 --	effects on offspring were more marked than on non-pre-natally exposed controls.	Iwanaga, E., et al, 1970
Mouse(F)	500ppm, 7h/day 9 days	inhalation	days 6-15	decr. fetal body wt. no change in preg. inud, average number of live fetuses, resorption	Murray, F.J. et al, 1979
Mouse(F)	.3 ml/kg .5 ml/kg	gav gav	days 6-15 day 6-15	decr. fetal wt incr. maternal mortality embryo death decr. fetal wt.	Naurot, P.S. & Staples,R.E. 1979*
	1 ml/kg	gav	day 6-15 or day 12-15	incr. maternal mortality embryo death decr. fetal wt. no increase in malformations seen at any dose level	

*cited by Barlow, S.M., Sullivan, F.M., 1982

SOLVENTS--Benzene

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
Rat(M) effects also seen in guinea pig and rabbit)	80 or 88 ppm for 7/h day, 5 day/wk for 30-40 weeks	inhalation	--	incr. testicular wt., degeneration of seminiferous epithelium of testes	Wolf, M.A. et al, 1956*
Rabbit(F)	0.25 mk/kg/day of 40% solution	s.c.	throughout	no effect on length of gestation, abortion rate, neonatal mortality, and anomaly rate	De Soilla, H, et al, 1963*
Rat(F)	0.1 k/kg throughout pregnancy	s.c.	throughout	no effect on length of pregnancy, maternal body wt, litter size or neonatal mortality	DeSoille, H., et al, 1965*
Rat(F)	0.3-20ppm for 10-15 days, pre-mating & throughout pregnancy	inhalation	throughout	no change in newborn body weight	Gofmekler, V.A. et al, 1968*
Rat(F)	210 ppm 10-15 days	inhalation	pre-mating & during mating & afterward	no pregnancy occurred	Gofmekler, V.A. Pushkina, N.N. et al, 1968
Rat(M,F)	0.5 or 1.0 ml/kg	s.c.	--	at .5 ml/kg level incr. chromosome aberrations in males at 24h at 1.0 ml/kg level incr. chromosomal aberrations in males and females at 24h	Dean, B.J. 1969*
Rat(M,F)	2 ml/kg	s.c.	--	incr. chromosome aberrations in male and female	Philip, P. & Jensen, M.K. 1970*

*cited by Barlow, S.M., Sullivan, F.M., 1982

SOLVENTS--Benzene

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
Rat(F)	1.6 ppm(4 mo)	inhalation	pre-pregnancy	incr. pre-implantation losses	Avilova, G.G & Ulamova, I.P., 1975*
	9.4ppm (4 mo)	inhalation	pre-pregnancy	incr. fetal hemorrhage postnatal mortality	
Rat(F)	1.6 ppm (4 mo)	inhalation	--	decr. length of estrus cycle	Avilova, G.G. & Ulanova,I.P.. 1975*
	9.4 ppm (4 mo)	inhalation	--	incr. duration of estrus	
Rat(M,F)	94 ppm during 4 mo.	inhalation	--	incr. chromosome aberrations	Dobrokhotov, B. & Enikau, M.I. 1977*
Rat(F)	3.3 ppm for 24 h/day	inhalation	days 9014	decr. maternal wt. gain fetal wt. incr. retarded ossification abnormal fusion of sternebrae, extra ribs	Hudak, A. & Ungvary,B.1978
Rat(F)	100,300 or 2200 ppm for 6 hr/day	inhalation	days 6-15	decr. maternal wt. gain in 2200 ppm group fetal wt in 2200 ppm group incr.skeletal anomalies in all groups with some preponderance in female offspring	Green, J.O. et al,1978*
Rat(F)	150,450,1500, 3000 mg/m^3, 24 h/day (7 days)	inhalation	days 7-14	150mg-decr. placental & fetal wt. 450mg--decr. placental & fetal wt, int. retard fetuses, incr. fetal loss, skeletal retar; wt retard fetuses	Tatrai, E. et al, 1980

*cited by Barlow, S.M., Sullivan, F.M., 1982

SOLVENTS--Benzene

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
Rat(F)	10,50,500 ppm (9 days)	inhalation	days 6-15	50 and 500 ppm dose decr. fetal body wt. incr. skeletal and visceral variants 500 ppm dose, decr. fetal length	Kuna, R.A. & Kapp, R.W. 1981
Guinea Pig (F)	.1 g/kg of 50% solution	s.c.	throughout	no effect on maternal body wt., length of gestation, number of offspring, offspring wt. or neonatal mortality	DeSoille, H. et al, 1967*
Rabbit (M,F)	.2 ml/kg./day (18 weeks)	s.c.inj.	--	incr.chromosome aberrations	Kissling, M., & Speck,B. 1971*
Rabbit (F)	500 ppm for 7 h/day	inhalation	days 6-18	incr. consumption of food and water decr. number of extra 13th rib anomalies no effects on implants, fetus number, resorptions, fetal body wt., malformations	Murray,F.J., et al., 1979

*cited by Barlow, S.M., Sullivan, F.M., 1982

SOLVENTS --Carbon Disulfide/EGME

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
			Carbon Disulfide		
Rat (M)	250mg/kg every 2nd day for 60 days	i.p.	--	testicular damage decr. spermatozoa	Gondzik, M., 1971
	25.0 mg/kg every 2nd day for 120 days	i.p.	--	irreversible destruction of testicular tissue decr. spermatozoa	
Rat (M,F)	10 mg/m^3 70-90 days	not given	days 1-20	persistent reduction in mitotic activity of liver cells of embryos and in epithelial cells of kidneys male: incr. aberrations in bone marrow cells	Barilyak, I.R. Vasilkleva, N.A 1974 (Abstract)
Rat (F)	0.03 or 10 mg/m^3	inhalation	not given	offspring: no congenital malformations	Tabacova, S., Balabaeva, L. 1980
			EGME		
Mouse (F)	31.25, 62.5, 125, 250, 500 or 1000 mg/kg/day (7 days)	gastric intubation	days 7-14	Dose-response incr. fetal death, gross anomalies skeletal anomalies, retarded skeletal ossification decr. fetal weight	Nagano, K., et al, 1981
Rat (M)	50,100,250, or 500 mg/kg/day (6° or 24°) for 2, 4,7, or 11 days	p.o.	--	500 mg/kg, decr. test. wt. prost. wt.	Foster, P.M. et al,

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
Rat(M,F)	30, 100,300 ppm 6h.day for 13 wks	inhalation	pre-gest	no effect on fertility litter size, pup wt., survival index, sex ratio	Rao, K.S., et al, 1983
Rat(M,F)	F:100 or 300 ppm 6h/day for 12 days M: 100 or 300 ppm 6 h/day for 10 days	inhalation	days 6-17	100 ppm-F decr. litter size no, live pups at birth, survival to 3 days put wt at day 3 incr. gest. time 300 ppm-F decr. maternal wt gain no litters produced. 300 ppm-M decr. testes size with atrophic tubules	Doe,J.E. et al, 1983
			Styrene		
Mouse(F)	250ppm, 6h/day (10 days)	inhalation	days 6-16	no effects on implants/ dam, live fetuses/dam incr. resorption rate	Kan Kaanpaa, J.T.J., et al, 1980*
Rat(F)	1.18 or 11.8ppm (4 mos)	inhalation	--	incr. length of estrus cycle duration of estrus	Layumova,A.S. 1972*
Rat(F)	300 or 600 ppm 7 hr day(9days) or 90 or 150 mg/ kg 2 times/day (9 days)	inhalation gav.	days 6-15 days 6-15	no effect on no, litters implant,live fetus/litter resporptions, fetal body wt, fetal crown to rump length, cong. anomalies	Murray, F.J., et al, 1978
Rat(M,F)	125,250 ppm	p.o.(water)	throughout 3 generations	no effects seen in fertility, no pups born,litter size,pup survival & body wt.,sex ratio, liver, kidney wt.& cytogenics of bone marrow cells	Manufacturing Chemists Asso., 1979*

*cited by Barlow, S.M., Sullivan, F.M., 1982

SOLVENTS--Styrene, Tolvene, Xylene

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
Hamster (F)	300,500,750 or 1000ppm, 6/hr day (12 days)	inhalation	days 6-18	300,500,750 ppm, no effects on implants/dam, live fetuses/dam or resorptions/dam at 1000 ppm-incr. resportions	Kankaapaa, J.T.J. et al, 1980*
Rabbit (F)	300 or 600ppm 7h/day (12 days)	inhalation	days 6-18	no effect on litter no. implant, live fetus/litter, resorp., fetal body wt., ft. crown to rump length, congen. malf.	Murray, F.J., et al, 1978
			Tolvene		
Mouse (F)	133 or 399 ppm, 24h/day (7 days)	inhalation	days6-13	at 133 ppm decr. fetal wt., no effects on implants/dam, live fetuses/dam, dead and resorbed fetuses/dam, malformations or anomalies	Hudak, A., & Ungvary, G., 1978*
Mouse (F)	0.3,0.5,or1.0 ml/kg	gav.	days 6-15	incr. embioplethality, cleft in 1.0 group decr. fetal wt in 0.5 and 1.0 groups	Nawrot, P.S. & Stapes, R.E. 1979*
	10 ml/kg	gav.	days 12-15	no effects on offspring	
Rat (F)	1500mg/m^3 for 24 h/day (5days)	inhalation	days 9-14	retard.fet. dev. incr. skeletal anomaly, extra ribs, fused sternebrae	Hudak, A., and Ungvary, G., 1978
	1500mg/m^3 for 24 h/day (8 days)		days 1-8		
	1000 mg/m^3 for 8h/day (21 days)				
			Xylene		
Rat (F)	115ppm, 24h/day (20 days)	inhalation	days 1-20	incr. in pre-implant losses in post implant losses no teratogenic effects	Krotov, Y.A. & Chafotar, N.A. 1972*

*cited by Barlow, S.M., Sullivan, F.M., 1982

SOLVENTS--Xylene

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
Rat(F)	0.15 or 0.4 g/kg	s.c.	days 1-10 or dats 1-18	daysl-10 in both groups incr. pre-implant, losses days 1-18 in 0.4 groups incr. pre and post-implant losses decr. fetal body wt. in both groups	Teshma, O.V., 1974*
Rat(F)	230ppm 24/h/day 5 (days)	inhalation	days 9-14	incr. skeletal anomalies (extra ribs, fused sternebrae) no effects on implants/dam, live fetuses/dam, dead or resorbed fetuses/dam, or fetal wt.	Hudak, A., & Ungvary, G., 1978
Rat(F)	35,350,700ppm 24th/day (7 days)	inhalation	days 7-14	in all groups, decr. placental wt. retard. ossific. in 700 ppm group, decr. maternal food cons. litter size, fetal wt. incr. post-implant losses freq. of extra ribs	Ungvary, G. et al., 1979
Rat(F)	150,1500,or 3000 mg/m^3 for 24h/day (7 days)	inhalation	days 7-14	dose-response effect decr. plac.&fet. wt., incid. preg., no implants litter size. incr. skeletal retardation skeletal anomaly, post-implant fetal loss	Ungvary, G., 1981
Rat(F)	10,50,500 mg/m^3 for 6h/day, 5d/wk (3 wks)	inhalation	days 1-21	50 and 500, incr. post-implant losses autolysis of implants hemorrhages decr. fetal wt.	Mirkova, E., et al, 1983

*cited by Barlow, S.M., Sullivan, F.M., 1982

VINYL CHLORIDE

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
Vinyl Chloride					
Mouse (M)	3000, 10,000, 30,000 ppm 6hr/ day for 5 days	inhalation	prior to mating	decr. implantation & incr. preimplantation loss in week 5 mating at 30,000 ppm, no dominant lethal effects	Anderson, D., et al. 1972
Mouse (F)	50 or 500 ppm w/15% ethonol 7 hr/day	inhalation	days 6-15	no effect at 50 ppm except incr. in fetal length at 500 ppm, incr. resorptions & skeletal anomalies, decr. litter size	John, J.A. et al, 1977
Mouse (F)	20, 500 ppm 7 hr/day	inhalation	days6-15	incr. fetal length at 50ppm incr. resorptions, skeletal anomalies, decr.fetal wt & length & live fetus/litter at 500 ppm.	John, J.A. etal 1981
Rat (F)	500 or 2500 ppm 7 hr/day	inhalation	days6-15	decr.maternal wt. gain, & fetal body wt., no. corpora lutea/dam at 500 ppm decr. maternal wt. gain fetal body wt. & Length incr. no. corpora lutea/dam & Incidence of dilated ureter, lumbar spurs & cervical vertebrae defects at 2500ppm	John, J.A. et al 1977
Rat (M)	0, 50,250, 1000 ppm, 6hr/day, 5 days/wk for 11 wks	inhalation	while mating	decr. mating in males at 2500 ppm & fertility at all doses no effects on implants/dam on testes, or accessory organs	Short, R.D., et al, 1977*

*cited by Barlow, S.M., Sullivan, F.M., 1982

VINYL CHLORIDE

SPECIES	EXPOSURE DOSE AND LENGTH OF EXPOSURE	ROUTE OF EXPOSURE	TIME OF GESTATION	EFFECTS	REFERENCE
Rats(F)	5500, 18,000, 33,000 mg/m^3 vapor/2.5hrs	inhalation	day 18	no effect noted in offspring vinyl chloride found in maternal and fetal blood, and amniotic fluid.	Ungvary, G. et al, 1978 (abstract)
Rat(F)	500,2500 ppm 7 hr/day	inhalation	days6-15	decr. fetal length & wt. incr. skeletal anomalies at 500 ppm and 2500 ppm	John, J.A. et al 1981
Rabbit(F)	500 or 2500ppm 7 hr/day	inhalation	days 6-15	decr. no live fetuses/litter incr. incidence delayed ossification of stenebrae at 500 ppm incr. resorptions; no gross anomalies observed at 2500 ppm	John, J.A. et al, 1977
Rabbit(f)	500,2500ppm	inhalation	days 6-18	decr. no live fetuses/litter incr. skeletal anomalies at 500 ppm	John, J.A. etal 1981

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WORKPLACE PHYSICAL FACTORS AFFECTING HUMAN REPRODUCTIVE FUNCTION

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INTRODUCTION

The following report addresses the numerous physical forces that occur in occupational settings, and presents the available evidence regarding their reproductive hazard potential. The discussion is organized to first describe the physical factors of the workplace environment. A review of specific adverse reproductive effects known or believed to be associated with exposure to these physical factors follows. Evidence for adverse effects on the reproductive process in women (including the fetus) and men are considered separately. Supporting data from studies with laboratory animals exposed to various physical forces under controlled conditions are presented last.

PHYSICAL FACTORS OCCURRING IN THE WORKPLACE ENVIRONMENT

The prevalence of various physical forces in the workplace is so widespread that essentially no occupation may be considered free from exposure. The difficulty in assessing the effects of physical forces on the reproductive cycle stems from the diversity of factors that may affect physiologic function. Most physical forces of health-related concern occur naturally in the environment, although their intensity or duration may be considerably magnified within the workplace. Therefore, an evaluation of the possible health consequences of physical forces requires an understanding of the nature of occupational exposures and how they relate to similar forces in everyday life. The physical factors that have most often been considered as potential occupational hazards include ionizing radiation, optical radiation, radiofrequency/microwave radiation, electric and magnetic fields, atmospheric pressure, hot or cold environments, noise, and vibration.

A. Ionizing Radiation

Ionizing radiation is energy that is transmitted in wave or particle form and is capable of causing ionization (ejecting orbital electrons) of atoms or molecules in the irradiated material. Alpha particles and beta particles are forms of ionizing radiation that interact directly with the irradiated material to cause ionization, whereas gamma rays and x-rays are a form of electromagnetic radiation that generate secondary particles in the irradiated material which subsequently lead to ionization. High-energy accelerators produce, in addition to x-rays and gamma rays, protons and neutrons which are effective in producing tissue ionization either directly (protons) or indirectly (neutrons). The critical element for understanding the biologic effect of ionizing radiation is energy deposition (i.e., absorbed dose), since the different types of ionizing radiation vary in their penetrative powers and number of ions produced. The unit used to quantify the energy deposited in matter by ionizing radiation is the rad, and is defined as 0.01 joules per kilogram of irradiated material. However, since different types of radiation can deposit the same total energy but produce different amounts of damage, a different unit, the rem, is used to quantify the degree of biologic damage. Rems are equal to a factor Q times rads, where Q is equal to 1 for x-rays and gamma rays, and Q is equal to 10 for alpha particles. Thus, at equivalent energy depositions, the alpha particle will produce ten times the biologic damage of x- and gamma rays. The currently recommended limit set by the Nuclear Regulatory Commission (NRC, 1977) and the National Council on Radiation Protection and Measurements (NRCP, 1971) for worker exposure to ionizing radiation is 5 rems/year for the whole body, or head and trunk, lens of the eyes, gonads or blood-forming organs. The cumulative lifetime limit is expressed as 5(N-18)rems, where N is equal to the worker's age in years.

The greatest contributor to human exposure of ionizing radiation is natural background radiation. The two sources of this exposure are cosmic radiation produced by collisions of high-energy particles impinging on the earth's atmosphere, and radionuclides (e.g., radon, potassium-40) which are commonly found in soil, brick, concrete, and stone. The total whole body radiation due to natural sources averages about 100 millirems per year; the average gonadal dose of natural radiation is about 80 millirems per year (National Academy of Sciences, 1980). Added to this exposure from background radiation is the dose received from medical use of x-rays, which contributes about 20 millirems per year to the gonadal exposure. Other minor sources of manmade exposure are atmospheric weapons testing, nuclear operations, consumer products, and building materials. Tobacco smoking may also result in substantial localized radiation exposures to points within the respiratory tract, possibly reaching 8000 millirems per year. (National Academy of Sciences, 1980).

Occupational Exposure to Ionizing Radiation

Use of ionizing radiation in industrial processes is a relatively recent, although rapidly expanding, practice. With the exception of radium dial painters and uranium miners, few incidents have been recorded of radiation injuries in the workplace. Traditionally, occupations associated with potential exposure to ionizing radiation were engaged in the use of x-ray machines, particularly for medical applications. The medical uses of x-rays have expanded considerably in diagnostic applications, particularly with the development of computerized axial tomography (CAT scanning) which has increased the precision of internal body-structure imaging. Further advances have also been made in the use of radionuclides administered internally for the purpose of organ imaging or tumor therapy. Essentially all hospitals and large medical clinics employ x-ray machines and/or radionuclides for routine medical procedures. Precautions taken to control exposure are necessarily strict, as are the safety requirements to be met by x-ray equipment.

Today, the industrial use of ionizing radiation is rapidly expanding both in terms of its application to industrial processes and the type of industry involved. Established applications for ionizing radiation in industry are summarized in Table 1. As the table illustrates, there are few segments of modern industry that do not employ some type of device or process that relies upon a source of ionizing radiation.

TABLE 1

Some Applications of Ionizing Radiation in Industry

Process or Device	Radiation Source(s)	Applications
Radiation Gauges	X-ray machine, gamma rays from a radioactive material (e.g., cesium-137, cobalt-60), beta emitters (e.g., strontium-90), neutrons.	Process control for automated production lines in many industries; density and moisture determinations; determination of coating thickness; monitoring of stack emissions from coal combustion.
Field Radiography	Gamma rays from a radioactive material (e.g., cobalt-60, iridium-192), x-ray machine.	Weld inspection; visualization of defects in fabricated steel, brass, copper and bronze.
Stationary Radiography	Convential (250 kV) and high voltage (1-10 million V) x-ray machine.	Internal structural examination of fabricated metal parts.
Fluoroscopy	X-ray machines	Instant viewing of internal structure of mass-produced components (e.g., transistors, cables, turbine blades); security inspection of luggage at airports.
X-Ray Diffraction and Fluorescence	X-ray machine plus a source of photons (e.g., iron-55, cobalt-60, cadmium-109, americium-241).	Determination of crystalline structure of fabricated products (e.g., turbine blades) to ensure absence of defects; elemental analysis of a specimen.

TABLE 1 (cont.)

Process or Device	Radiation Source(s)	Applications
Electron Beam Evaporators	Electron beam from a cathode	Evaporation of refractory metals (e.g., tungsten, tantalum, molybdenum) and nonmetals (e.g., quartz, alumiunum oxide) to provide thin coatings on materials.
Electron Beam Welder	Electron beam from a cathode	Welding of refractory metals and non metals.
Radiation Processing	Gamma rays from a radioactive material (e.g., cobalt-60), electron-accelerator.	Sterilization of food and medical supplies; controlled degradation and crosslinking of plastics; treatment of wood/plastic composites for strength and appearance; disinfection of hides and wool.

Future developments in the industrial application of ionizing radiation are likely to be focused in the area of radiation processing. In the chemical industry, and in the production of flooring, furniture, textiles, adhesives, paints, membranes, and wood/plastic composites, research is being conducted on radiation processing to achieve cross-linking, polymerization, grafting and free-radical generation (Bradley, 1983). Preservation and disinfection of foods, spices cosmetics and pharmaceuticals by irradiation is also rapidly approaching large scale commercial application (Porter, 1984; Bradley, 1983). The radiation source used in disinfection can be either a machine-generated electron beam or gamma rays from cobalt-60 or cesium-137 (Porter, 1984). Concern for worker exposures occurring during radiation processing operations is greater than for other industrial or medical applications. Problems can be forseen due to the experimental nature of the processes, the high doses of radiation employed, the likelihood that radiation processing will be conducted in small establishments with limited resources for protective measures, the lack of employee training regarding the hazards involved, and the absence of regulatory standards and guidelines for controlling exposure. In contrast with many industrial applications where radiation doses are relatively low, preservation and sterilization require large dose applications. Reduction of microbial load and improvement in food properties occurs with applications of about 100,000-1,000,000 rads, and sterilization for commercial purposes require about 1 to 5 million rads (Porter, 1984).

B. Nonionizing Radiation

The term nonionizing radiation refers to the region of the electromagnetic spectrum where the energy of the emitted photons is incapable of ionizing atoms or molecules in the irradiated material. The lower wavelength limit for nonionizing radiation is considered to be 100 nanometers (nm), which corresponds to ultraviolet light. Succeeding portions of the spectrum correspond to visible light (400-750 nm wavelength), infrared radiation (0.75 micrometers (µm) - 750 nm wavelength), and radiofrequency radiation (1 millimeters (mm) - 10,000 kilometers (km) wavelength). As wavelength increases along the electromagnetic spectrum, wave frequency decreases. There exists considerable confusion arising from the fact that the anxiety-provoking term "radiation" is applied to x-rays (i.e., ionizing radiation) as well as microwaves, radio and television transmission signals, and other forms of nonionizing energy. Actually, these forms of energy are significantly different with respect to biologic activity. All humans are under constant exposure to natural or manmade sources of nonionizing radiation, thereby complicating the design of any population study attempting to assess the health effects in exposed versus nonexposed individuals.

Ultraviolet Radiation

Ultraviolet radiation is produced naturally by the sun, and artificially by arcs operating at high temperature. Exposure to ultraviolet radiation in the workplace is associated with incandescent, fluorescent and discharge type light sources, as well as welding and cutting torches, electric arc furnaces, plasma torches and lasers. In addition, outdoor workers, such as farmers, fisherman, and construction workers, receive substantial solar exposures. Ultraviolet radiation can be expected to occur in all occupations involving germicidal lamps, welding arcs and plasma torches, and in many industrial drying and curing processes, printing processes, non-destructive testing, and chemical manufacturing operations.

Visible Light

Visible light is provided by the sun and artificial light sources. In addition to visible light required for illumination, industrial exposure to visible light is associated with highly incandescent bodies and various types of arc processes. Many sources of high intensity visible light also produce substantial thermal energy.

Infrared Radiation

All objects emit infrared radiation, which increases as a function of temperature. The sun is a major source of infrared radiation. Occupational exposure occurs either directly from lamps or indirectly from heat sources. The most widely recognized industrial exposures to infrared radiation are from hot furnaces, molten metals or glass, and arc processes.

Radiofrequency/Microwave Radiation

Typical radiofrequency/microwave electromagnetic radiation covers frequencies from about 10 hertz (Hz) (1 Hz = 1 cycle per second) to 300,000 megahertz (MHz), which corresponds to wavelengths from 100,000 km to 1 mm. The application of these manmade electromagnetic fields is extremely diverse and rapidly expanding. Modern applications of radiofrequency/microwave radiation are in radio and television broadcasting, communications (long distance telephone, two-way radio), radionavigation (ships, aircraft, spacecraft), radar (military and civilian use, weather surveillance), heating (food preparation, industrial drying and sealing processes), and medicine (diagnosis, diathermy treatment). In terms of potential health effects two frequency ranges are receiving focused attention. One is the microwave and shortwave frequency range (several MHz to 100 gigahertz (GHz)) used by the military and for communications. The other is the extremely low frequency range (10-60 Hz) associated with high voltage power lines and considered for use in naval communications.

The energy level of radiofrequency/microwave radiation is measured with electric or magnetic field strength meters, or with a power meter. From a biological standpoint, the important measure of energy is the power density in milliwatts (mW)/cm^2 or watts (W)/m^2, or the dose of absorbed energy per unit time per unit mass, such as mW/g or W/kg. Many people are familiar with the transformation of electromagnetic radiation into heat, such as that which occurs in a microwave oven. In order for an object to be heated by electromagnetic radiation, it must have a diameter equal to at least one-tenth of the wavelength (Mikolajczyk, 1982). For a human, significant heating will not occur with radiofrequency radiation having a frequency below 15 MHz and a wavelength greater than about 20 m (i.e., television and radio transmission, radiation from power lines). The electromagnetic radiation used in radars is in the microwave frequency range capable of inducing thermal and subthermal biologic effects in humans. A large parobolic radar antenna loaded from a 500 kW transmitter is capable of producing 1000 mW/cm^2 "hot spots" in its field, which is comparable to the power density inside a microwave oven (Mikolajczyk, 1982). The American National Standards Institute Committee C95 has recently proposed revised guidelines (ANSI C95.1-1982) for safe exposure to radiofrequency electromagnetic fields which acknowledge that prolonged whole-body exposure at intensities above 100 mW/cm^2 are dangerous at frequencies for which significant energy is coupled to the human body. In humans, the radiation absorption efficiency reaches a maximum at a frequency of 77 MHz for a 1.75 m tall person weighing 70 kg (Gandhi, 1975). NIOSH (1977) has estimated that the majority of industrial radiofrequency sources operate from

10-40 MHz, whereas a microwave oven operates at 2450 MHz (Brent, 1983). Diathermy electromagnetic waves (27.5 MHz) have great penetration into the human body and produce signficant heating, while microwaves with frequencies above 10,000 MHz have little penetration (Brent, 1983). The latest recommended exposure limits for radiofrequency/microwave radiation made by the American Conference of Governmental Industrial Hygienists (ACGIH, 1980) specify a permissible power density of 100 mW/cm^2 for frequencies of 10 kHz to 3 MHz, 1 mW/cm^2 for frequencies of 30 MHz to 100 MHz, and 10 mW/cm^2 for frequencies of 1 GHz to 300 GHz.

Workplaces designated as hazardous due to the presence of radiofrequency/microwave radiation are generally associated with antenna systems, emitters, generator tubes and other high frequency units. The adverse health effects from exposure to radiofrequency/microwave radiation that result in tissue heating are well-documented (NIOSH, 1977). Chronic effects from subthermal doses remain unclear, particularly with respect to low frequency and weak-field radiation.

Laser Radiation

A laser (acronym for "light amplification by stimulated emission of radiation) operates in the infrared, visible, and ultraviolet regions of the electromagnetic spectrum. Lasers are stable sources of monochromatic optical-frequency waves, where output can be collimated to form a beam with extremely high power densities. The power density of a focused laser beam can exceed 100 MW/cm^2 (Goldman, 1983). The source of laser radiation can come from a solid, liquid, or gas that can be made to fluoresce. Sources being used include ruby, neodymium, helium, neon, argon, krypton, carbon dioxide, and an yttrium-aluminum-garnet combination.

The laser has found great value in numerous segments of industry, and its uses are continuing to expand. In the biomedical field, lasers are used as a kind of optical knife to perform delicate surgery, and also in the detection of tumors, and to measure blood circulation and elements in the blood. Several methods have recently been developed where lasers are used for the detection of air pollutants with great specificity and sensitivity. Lasers are used in metalworking and in the aircraft industry to drill holes, particularly on curved surfaces, with great accuracy and precision. A recent development in laser applications is in communications and information transfer with fiber optics.

The major health hazard associated with the use of lasers is burns to the skin and eyes. Whereas lasers operating in the visible or near infrared wavelength regions may produce severe retinal burns of the eye, lasers operating in the infrared region (e.g., carbon dioxide laser) may produce surface burns on the cornea of the eye.

Ultrasound

Ultrasound is a mechanical vibration of an elastic medium having a frequency range beyond 16,000-20,000 Hz, which is above the audible frequency for the human ear. Low frequency ultrasound (18,000-30,000 Hz) of high intensity (6-7 W/cm^2) is widely used in industry in cleaning baths for metal and fabricated parts, in welding, brazing, and soldering, for electrolytic coating, and for acceleration of chemical reactions. Low frequency ultrasound is also a component of the noise produced by jet engines, gas turbines, and powerful pneumatic devices.

High frequency ultrasound is more readily absorbed by the surrounding medium and does not propogate in air. Penetration of human tissue by ultrasound decreases as the frequency increases. High frequency ultrasound (500 kHz - 5 MHz) of low intensity (0.1-2.0 W/cm^2) is widely used for detection of flaws and structural analysis of matter.

The medical applications of ultrasound have greatly increased in recent years, particularly in obstetrical diagnostic procedures (Levi, 1976). Two types of ultrasound are used with pregnant women. One is pulsed ultrasound, employing frequencies in the 1-10 MHz range with output intensities ranging from <1-10 mW/cm^2 The other is continuous wave ultrasound, employing frequencies of about 2 MHz with output intensities ranging from <1-20 mW/cm^2. Continuous wave ultrasound is used early in pregnancy for monitoring fetal function or distress; pulsed ultrasound is used later in pregnancy for placental localization, confirmation of normal or abnormal pregnancy, detection of twins, and in monitoring fetal growth.

Worker exposure to ultrasound, particularly when loading and unloading parts cleaning tanks, may result in damage to the peripheral nerves and vasculature of the fingers, hands and forearms (Roscin, 1983). The adverse effects in humans from high frequency ultrasound are not clearly understood.

Video Display Terminals

Use of video display terminals (VDTs) is rapidly expanding as a means to display alphanumeric information in the workplace. An estimated 5-10 million VDTs were in use in the United States by 1980 (NAS, 1983). By 1910, it is projected that 25 million VDTs will be in use (Arndt and Chapman, 1984). The principal applications for VDTs are for data entry, data acquisition, interactive communication, word processing, computer programming, computer-assisted design, and computer-assisted manufacture. The expanding use of VDTs has created an area of special health concern with respect to workplaces and occupations that were traditionally regarded as hazard-free. The major issue of concern is the potential for chronic worker exposure to radiation emitted by VDTs and its possible health-related consequences.

Most VDTs use cathode ray tubes, and in many respects are similar to television receivers. Cathode ray tubes emit visible radiation (light), but also emit ultraviolet and infrared radiation, and radiofrequency radiation in the 15-125 kHz frequency range. Cathode ray tubes also produce internal x-rays which are effectively filtered by the tube face, thus preventing most emissions. Numerous field surveys and laboratory studies by industry, government, and independent groups have concluded that the emission of all types of radiation by VDTs is well within acceptable limits of exposure (NAS, 1983; Arndt and Chapman, 1984). It should be noted, however, that most VDT emissions are in the radiofrequency range below 300 kHz, where no enforceable emission standards have been established and adverse health effects are not well understood. A current recommended limit of 614 V/M or 100 mW/cm^2 for radiofrequencies between 10 kHz and 3 MHz is being made by the American Conference of Governmental Industrial Hygienists (1980). This level is about ten times higher than the VDT emissions in the 10 kHz-100 MHz range measured under worst-case conditions in a study by the Bureau of Radiological Health (NAS, 1983). In the same study, no x-ray emissions could be detected from 91 VDT units operated under normal conditions.

Magnetic Fields

Magnetic fields are associated with power transmission lines, electric machinery and appliances, and the Earth's natural electric field. Beyond the near field region, an electric field is always associated with a complementary magnetic field, and vice versa. With the exception of static fields such as the Earth's magnetic field, all fields alternate as a function of time, thereby exhibiting a measureable pulse duration. For practical purposes, a magnetic field is considered static if it has a frequency of oscillation of less than 1 mHz or a pulse duration of more than 1 ks (about 16 minutes). Magnetic field strength is measured as magnetic flux per unit area, expressed as Tesla (T) or Gauss (G)

The magnetic field strength directly beneath a 60 Hz alternating current (AC) power transmission line ranges from .3 to .6 G, dropping off to about 0.01 to 0.1 G 200 feet from the right-of-way center (Dodge, 1984). By comparison, the Earth's natural magnetic field strength is .6 G, and localized 60 Hz magnetic fields around household appliances (e.g., color television and hair dryers) may range from 1 to 25 G. It is generally assumed that the biological effects of magnetic fields are attributable to induced body voltage, electric fields, and currents.

C. Hyperbaric and Hypobaric Environments

Air pressures in excess of those found at sea level (14.7 pounds/square inch) are considered hyperbaric, and air pressures below that found at sea level are hypobaric. Workers exposed to hyperbaric environments include those engaged in caisson or tunneling operations, where compressed gas is used to exclude water or mud, and to provide structural support during construction. Such operations are associated with pressures that can range to more than four times that occurring at sea level (NIOSH, 1977). Underwater diving can be associated with considerable pressures, since each 10 meter increase in sea water depth is equivalent to an increase of one atmosphere pressure. The primary health effect caused by hyperbaric environments is the tissue damage that results from expansion or contraction of gas spaces found within or adjacent to the body, such as around the teeth, in the sinuses and within the ear. This type of effect is referred to as barotrauma. Other secondary types of damage caused by hyperbaric environments result from the narcotic action of nitrogen at four atmospheres of pressure or more, oxygen poisoning when its partial pressure exceeds two atmospheres, and the severe effects from rapid decompression.

Hypobaric environments can be of two types, high altitude and low altitude. High altitude hypobaric environments occur with pilots and air crews operating aircraft at altitudes in excess of 30,000 feet. In these situations, the greatest hazard is from hypoxia caused by lack of oxygen. At lower altitudes, hypoxia also occurs, as evidenced by the syndrome of impaired judgement and performance, and general feeling of malaise associated with acute mountain sickness (NIOSH, 1977).

D. Hot Environments

The relationship of body heat to the external environment is a function of air temperature, air velocity, moisture content of the air, and radiant temperature. The hazards of working in a hot environment result when an imbalance occurs between metabolic heat production and heat loss from the body to the environment; that is, heat loss fails to keep pace with heat gain by the body. A rise in the temperature of the body is an indication that the body is storing heat which it cannot dissipate. As a result of the body's inability to adequately dissipate heat, four primary illnesses may occur. In order of increasing severity they are referred to as heat rash, heat cramps, heat exhaustion, and heat stroke. Heat stroke is a serious medical condition which can be fatal if immediate action is not taken. It is recommended

(NIOSH, 1977) that workers should not continue to perform tasks that allow their body temperature to exceed 38°C.

E. Cold Environments

Maintenance of heat balance in a cold environment requires that the body limit heat loss and increase heat production. The primary mechanism for limiting heat loss is constriction of the blood vessels (vasoconstriction), particularly in the extremities. This results in a drop in skin temperature and consequently less heat loss to the environment. Under severe conditions, the chilling of the extremities is so great that tissue freezing occurs, which results in frostbite. Work in a cold environment of sufficient duration to result in exhaustion will make the individual more prone to heat loss and the development of severe acute effects of general body hypothermia (NIOSH, 1977).

F. Noise

Noise, generally identified as unwanted sound, is probably the most prevalent of all occupational hazards. Permanent, noise-induced hearing loss has been recognized for several hundred years (ACGIH, 1980). Noise is classified according to several criteria. Wide-band noise refers to sound that covers a large portion of the available frequency spectrum, and is typified by the noise produced by large machinery and jet engines. Narrow-band noises are often associated with a definite pitch, such as that produced by a circular saw or other power cutting tools. A noise of short duration (less than a second) that rises rapidly to a peak and then falls to below background levels is referred to as impulsive or impact noise. The noise from a gunshot or a forging hammer are examples of impulsive noise.

G. Vibration

Vibration occurs in all segments of industry where power driven tools, heavy machinery and mechanized equipment are utilized. When considering workplace exposures, vibration is usually categorized as either segmental or whole body vibration. Whole body vibration is mechanically transmitted to the entire human body through a supporting structure, such as a vehicle seat. Segmental vibration affects localized parts of the body, usually the hands or feet. Hand-operated tools are a common source of segmental vibration.

The harmful effects of segmental vibration seem to be more severe than for whole body vibration (NIOSH, 1977). Workers who use vibratory hand tools for prolonged periods may develop Raynaud's phenomenon ("dead hand" or "vibratory white fingers"). This condition is associated with numbness and blanching of the fingers, and can result in loss of muscular control and reduced sensitivity to vibration, pain and temperature. Numerous additional ailments can be associated with segmental vibration, including changes in bone, nerve degeneration, muscular weakness and atrophy, and Dupuytren's disease causing permanent flexion of one or more fingers (NIOSH, 1977).

ADVERSE EFFECTS OF WORKPLACE PHYSICAL FACTORS ON REPRODUCTIVE FUNCTION IN WOMEN

A. Effects Due to Radiation Exposure

Ionizing radiation is known to exert profound effects on reproduction. In the human female the reproductive process is susceptible to radiation induced damage in several ways. Female mammals are born with a fixed supply of oocytes (germ cells), that are continuously depleted throughout life by ovulation. Damaged germ cells cannot be replaced. Exposure of the germ cells to ionizing radiation, either during gestation (fetal life) or after birth can be manifested in reproductive disorders at puberty and during reproductive life. In addition, there is evidence that exposure to high-energy ionizing radiation during childhood may lead to disorders of the endocrine system, which subsequently give rise to infertility or failure to undergo normal pubertal development. Exposure of pregnant women to levels of greater than 20 rad leads to birth defects, while lower exposures in the region of 1-10 rad are associated with increased childhood leukemia and other cancers (NAS, 1980). The National Coucil on Radiation Protection and Measurements (NCRP, 1977) recommends that workplace exposure of a fertile woman be controlled to the extent that if she becomes pregnant her fetus will receive a cumulative exposure of no more than 0.5 rad.

Understanding of the teratogenic effects of large doses of ionizing radiation on fetal development dates to the explosion of the first nuclear weapon in 1945. Extensive retrospective epidemiologic surveys were conducted on individuals who were exposed to radiation *in utero* in Hiroshima and Nagasaki (Yamasaki et al., 1954a,b; Wood et al., 1967a,b; Brent, 1983; Sutow and West, 1955). These studies along with earlier case reports provide clear evidence of severe teratogenic effects, particularly the occurrence of microcephaly (congenital malformations of the brain) resulting from high doses of radiation during pregnancy (Brent, 1983). Of greater interest to present-day occupational settings, however, is the effect of low-level radiation exposure (both acute and chronic) to women of child-bearing age. However, no reports of harmful effects of ionizing radiation in the workplace on female reproductive function have been found.

Exposure to X-Rays During Fetal Life

The use of x-rays during obstetric examination of pregnant women (pelvimetry) has resulted in thousands of fetal exposures. Several major studies have indicated that the human embryo is especially sensitive to the leukemogenic effect of ionizing radiation (Brent, 1983; Diamond et al., 1973). It is estimated that a 1-2 rad *in utero* radiation exposure increases the risk of leukemia developing in the offspring by a factor of 1.5-2.0 over the natural incidence (Brent, 1983). In a major epidemiologic investigation, the Pelvimetry-Leukemia Study (Diamond et al., 1973), births from 20,000 mothers exposed to x-rays during pregnancy were identified in Baltimore, Maryland. These births were matched with unexposed control infants by race, sex, birth order, hospital of birth and dates of birth, and both sets of offspring followed up during childhood. A significant finding was that children exposed to x-rays *in utero* were more likely to develop leukemia than children born to mothers who had not received x-ray examinations during pregnancy.

In a related case-control study conducted in England, 7649 children who had died from cancer were compared with a cancer-free control group matched for sex, date of birth, and geographic region (Stewart and Kneale, 1970). Prenatal exposure to x-rays occurred in 1141 of the children in the cancer care group and in 744 of the children in the matched control group. An excess cancer risk from obstetric x-ray examination was indicated, which increased in direct proportion to the number of x-rays received by the mother. The risk for cancer development appeared to be greatest when maternal x-ray exposure occurred during the first trimester of pregnancy. The concept of increased risk with increasing dose is a fundamental tenet of toxicology, and hence when a positive "dose-response" relationship is identified in a population study the results merit serious consideration.

Several investigators have seriously questioned whether _in utero_ exposure to low doses of radiation increases the risk of leukemia. In support of this contention it is noted that children exposed _in utero_ at Hiroshima and Nagasaki did not develop increased numbers of leukemics, and that the risk of leukemia is greater in "unirradiated" siblings of leukemics than in offspring of women exposed to diagnostic x-rays before or during pregancy (Brent, 1983). These arguments raise the important issue that genetic and environmental factors may be of equal or greater importance in determining overall cancer risk than is prenatal exposure to diagnostic x-rays.

In addition to possible increased risk for cancer development, other studies of pregnant women exposed to x-rays have focused on possible effects on health, growth, development and reproductive experience of their offspring. From the Pelvimetry-Leukemia Study of Diamond et al. (1973) a subset of children exposed prenatally to x-rays, and their corresponding matched controls, born in the years 1947-1952 were evaluated by questionnaire during the period 1961-1967 (Meyer and Tonascia, 1973, 1981). The study population was chosen primarily for having an early age of reproduction, and because of the expectation that impaired reproductive function would be found in the group exposed to x-rays. The major finding in this study was that women exposed to x-rays in utero had more live births and stillbirths than controls, as well as earlier onset of menses and births at age 15 years or less. It is difficult to say whether any of these effects are definitely caused by prenatal exposure to x-rays, even though such variables as economic, social and medical factors were accounted for in the study. There is some evidence from animal studies that x-irradiation of fetal ovaries leads to accelerated oocyte maturation and temporarily increased fertility.

Dosages of x-rays to the fetus associated with pelvimetry of pregnant women is about 1-5 rads, depending upon the number of films taken. In addition to dosage of irradiation, the time of gestation when x-rays are administered may be of equal or greater importance to the development of adverse effects on the fetus. Brent (1983) has concluded that human growth retardation, microcephaly, and mental retardation are predominant observable effects when acute exposures to the fetus exceed 50 rads. The central nervous system of humans appears to be particularly susceptible to the effects of high doses of x-rays. This susceptibility has been explained by noting that the central nervous system is sensitive to radiation damage throughout gestation, while other organ systems show a much narrower period of susceptibility (Brent, 1983). Exposure of a fetus to a dose less than 10 rads is not believed to increase the risk of gross congenital malformations or fetal death, although the potential carcinogenic (leukemogenic) risk at this dose level remains a matter of controversy.

Exposure to X-Rays after Birth

The effect on future reproductive function from x-ray exposure of females at various ages is not well defined across a broad dose range. At very high doses, the effects of x-rays on ovarian function are clear. Because the ovary involves a fixed population of germ cells that cannot be replaced, x-ray induced destruction of oocytes leads to permanent sterility. This effect has been demonstrated in female children and adults receiving radiation therapy for malignancies (Shalet, 1983). Permanent menopause in women over 40 can be achieved by a total radiation exposure of about 6 million rads, and in young women the 50 percent probability dose for inducing permanent sterility is about 20 million rads over a six week period (Shalet, 1983). Pituitary gonadotropin deficiency caused by cranial irradiation treatment may also contribute to hypogonadism and subsequent infertility in females. Paradoxically, anovulatory sterility has been successfully treated in adult women with x-ray doses to the ovaries and pituitary in the range of 400 rads (Kaplan, 1958). This effect may be related to similar observations from animal studies where irradiation may accelerate the development of oocytes that survive the x-ray treatment.

Females receiving diagnostic x-rays to the abdominal region may experience reproductive disorders, although the available data are limited. Mondorf and Faber (1968) evaluated a small group (180) of women previously exposed to x-rays when receiving a barium enema as children. They looked only at the number of children born to these women, their sex ratio, and the age of the mother at time of birth. A control group was employed, although it was not adequately described. No differences could be found in fertility patterns between the irradiated and control groups.

Larger studies of adult women exposed to abdominal x-rays before pregnancy suggest an association with increased risk of chromosomal nondisjunction (mongolism) in their offspring. A retrospective study published in 1961 was the first to report an association between maternal abdominal irradiation prior to pregnancy and the incidence of mongolism. A more detailed prospective epidemiologic study was subsequently conducted which compared children born before and after diagnostic radiation exposure of the mother (Uchida et al., 1968). Prospective epidemiology studies, although generally more difficult to conduct than retrospective studies, provide the most unambiguous results. Chromosomal abnormalities, including mongolism, occurred with a significantly elevated frequency among the offspring of irradiated mothers. Furthermore, maternal susceptibility to the effects of x-rays on chromosome abnormalities appeared to increase with increasing age of the mother at time of irradiation. The results of this study are supported by the similar findings of a detailed retrospective study by Sigler et al. (1965), although they are in conflict with earlier retrospective studies (Carter et al., 1961; Schull and Neel, 1962). One of the difficulties in assessing the relationship between maternal irradiation and mongolism in subsequent offspring is the lack of a clear dose-response relationship. Accurate dose information is generally difficult or impossible to obtain from retrospective studies. In the only major prospective study on mongolism (Uchida et al., 1968), gonadal doses of irradiation were estimated and did not clearly indicate an association between exposure intensity and risk of mongolism.

Exposure to Optical Radiation (Ultraviolet, Visible, Infrared and Laser)

The harmful effects of optical radiation appear to be restricted to the surface of the body, especially the skin and eyes. Damage is primarily the result of tissue heating, which causes protein denaturation and the typical symptoms associated with burns. An additional biologic effect of ultraviolet and infrared radiation, and lasers is excitation of intracellular organelles unrelated to tissue heating (Dodge and Kainz, 1983). The health effects resulting from athermal excitation of cell organelles are not understood. Ultraviolet radiation is also regarded to be a cause of skin cancer. There are no known reproductive effects in humans or lower animals associated with occupational or environmental exposure to optical radiation.

Exposures to Radiofrequency/Microwave Radiation

Epidemiologic studies of microwave workers and military personnel exposed to radar have not provided clear evidence for the development of pathologic damage, reproductive failure in women, or malignancies (Michaelson, 1982). These negative, and in some cases equivocal, results may reflect inadequacies in the epidemiologic studies involving the lack of dose information, appropriate control groups, and recognition of concomitant exposure to toxic agents. Thus there is a need for well-designed and carefully controlled epidemiologic studies of workers and other populations exposed to measured amounts of radiofrequency/microwave radiation. The presently available data suggest that the adverse effects from radiofrequency/microwave exposure are primarily, if not exclusively, the result of tissue heating. Occupational exposure of women to radiofrequency/microwave radiation at typical power densities would not be expected to produce sufficient internal tissue heating to harm the fetus or the reproductive organs.

Rather extensive studies on the biologic effects of radiofrequency/microwave radiation have been conducted in recent years. Included in these studies are numerous case reports of human exposure and a few epidemiologic investigations. Michaelson (1982) reviewed several studies in which microwave heating of the female pelvic region was used to treat gonorrhea, pelvic inflammatory disease (before and during pregnancy), endometriosis, carcinoma of the uterus, or pelvic peritonitis. There did not appear to be any clear evidence that the microwave treatments interfered with ovulation, conception, and pregnancy, although most of the studies were not specifically designed to evaluate reproductive effects. In one major study, at least 2000 women were treated with microwave diathermy to relieve the pain of uterine contractions during labor. The children born to these patients were followed for one year, with no evidence being found for the development of adverse effects. A longer follow-up period would be required, however, to fully assess the effects of microwave exposure on growth and physiologic function.

Exposure to Ultrasound

The use of ultrasound for fetal monitoring and diagnosis raises legitimate questions of safety for both the mother and fetus. Thus far, the limited available data have not indicated a significant health threat from medical applications of ultrasound (Brent, 1983; Council on Scientific Affairs, 1984). From a small case-control study of congenital malformation and early death in infants born to physiotherapists in Sweden, occupational exposure to ultrasound was associated with 42% (14/33) of the cases and 27% (17/63) of the controls ($p=0.10$) (Kallen et al., 1982). These statistically non-significant results can only be considered as suggestive of an adverse reproductive effect associated with ultrasound, because of the small number of cases in the study. Ongoing epidemiologic studies of infants exposed _in utero_ to ultrasound may provide significant new information regarding the nature and magnitude of health risks (Brent, 1983).

Exposure to Electromagnetic Radiation from Video Display Terminals (VDT's)

Reports of clusters of spontaneous abortions, miscarriages, and birth defects among VDT operators raised serious concerns over safety. Although at least two of these clusters have been investigated, no association has been confirmed for VDT work and increased risk for adverse reproductive outcome (NAS, 1983). The only documented causative role of VDTs in inducing birth defects or fetal death comes from the fact that VDTs emit ionizing radiation, which has been implicated in birth defects and increased fetal death rates. Despite numerous studies on emissions from VDTs (NAS, 1983), none have reported levels of ionizing radiation that are known to be associated with biologic effects of any kind. Since the primary emissions from VDT's are below 300 kHz, the possibility exists that low level nonionizing radiofrequency radiation may be involved in some type of, as yet unexplained, adverse effect on reproduction. Great care should be taken in making any such inference however, since no clear evidence exists to support any such association. Moreover, the fostering of needless anxiety among female workers will further complicate any attempts at conducting unbiased studies concerning VDT health effects.

The National Institute for Occupational Safety and Health (NIOSH) has undertaken an extensive study that is designed to resolve the question of VDT effects on reproduction. The three-year study will involve a cohort of 2000 VDT-exposed women and 2000 controls who are not exposed (Industrial Safety and Hygiene News, August 1984). All women will be employed in non-management positions in a small geographic area. Reproductive, health, and work histories will be obtained by self-administered questionnaires, given at three

9-month intervals. Personal habits such as alcohol, tobacco, and caffeine use will be taken into account. NIOSH intends to perform a follow-up check to evaluate future reproductive outcomes.

Exposure to Magnetic Fields

Considerable interest has developed in recent years in evaluating the biologic activity of low-level low frequency (50-60 Hz) magnetic fields. Exposure to this type of electromagnetic radiation commonly occurs in the vicinity of high voltage power lines. The U.S. Navy has also proposed the development of extremely low frequency (ELF) communications antennas, which would result in signficant population exposures.

Teratogenic effects in humans have not been associated with exposure to magnetic fields. Several epidemiologic studies are responsible for the creation of a major public health issue, however, concerning exposure to electric and magnetic fields. The first study to generate controversy was a report of Russian switchyard workers who experienced various subjective symptoms, including diminished sex drive, associated with work in high voltage substations (reviewed by Knave et al., 1979). Subsequent studies in the United States, Sweden, England and Wales have reported correlations between increased incidences of leukemia and other concerns and presumed exposure to electric and magnetic fields near high voltage power lines (reviewed by Douglas, 1984 and Dodge, 1984). The relationship between leukemia and residency near power lines has been refuted in at least one study (Fulton et al., 1980). These reports must be interpretated with caution, however, since the demonstration of a correlation does not establish causation in any of these studies. The problem with most occupational and community epidemiology studies regarding magnetic fields is that exposure intensity is rarely measured, and other variables that may affect cancer susceptibility (e.g., diet, genetics, chemical exposure, etc.) are not adequately taken into account. Thus the available data regarding human health aspects of exposure to magnetic fields are inconclusive, although sufficient suggestive evidence exists to warrant further in-depth studies.

Exposure to Hyperbaric and Hypobaric Environments

Typical occupations involving women are not generally associated with substantially increased or decreased ambient pressures. Nevertheless, atmospheric conditions are known to affect the outcome of pregnancy. Several studies have documented that human birth rates are reduced at high altitudes and that birth weights are also decreased (Council on Scientific Affairs, 1984). At least one study suggests that infant mortality is greater at high altitudes (McCullough et al., 1977). All of these effects are believed to be related to fetal and maternal hypoxia from reduced ambient oxygen levels. There is no clear evidence for teratogenic effects covered by exposure of pregnant women to hypobaric (i.e. reduced atmospheric pressure) environments.

Data concerning the effects of hyperbaric environments on female reproduction are quite limited. Two recent reports have linked scuba diving during pregnancy with congenital malformation and reduced birth weight in the offspring (Bolton, 1980; Turner and Unsworth, 1982). These studies are based on only a few cases observed, although they appear sufficient to justify the avoidance of increased ambient pressures during pregnancy.

Exposure to Hot Environments

Experts have questioned whether women are exposed to work environments that are sufficiently hot to affect reproduction (Council on Scientific Affairs, 1984). Animal studies indicate that maternal temperature must be raised to at least 38.9°C (°F equivalent) before effects on the fetus are observed. Teratogenic effects have occurred in humans in conjunction with maternal hyperthermia. Prolonged fever in the mother during the first trimester of pregnancy appears to be a major factor in producing severe central nervous system dysfunction in the offspring (Clarren et al., 1979; Fisher and Smith, 1981; Pleet et al., 1981). In a few cases involving teratogenic effects in humans, it was postulated that maternal hyperthermia resulting from prolonged bathing in a hot tub or sauna may have been a causative factor. In a controlled study designed to explore this possibility, Harvey et al. (1981) found that among 20 women who volunteered to sit in a hot tub or sauna, none were able to tolerate it long enough for their vaginal temperature to exceed 38.9°C. Nevertheless, the authors suggested that guidelines be set for the duration of exposure of pregnant women to hot environments such as hot tubs and saunas.

Exposure to Cold Environments

There is no documentation available concerning the specific effects on reproductive function or pregnancy outcome in women exposed to cold environments. The absence of data, either positive or negative, concerning the relationship between cold environments and reproduction indicates the need for further study.

Exposure to Noise

Evidence concerning the effects of noise on reproductive function and pregnancy outcome in humans is largely circumstantial and conflicting. Reports of low birth weight, increased stillbirths and teratogenic effects have cited residence near noisy airports as a contributing factor. Jones and Tauscher (1978) analyzed birth certificate data from Los Angeles County, CA, and found higher rates of congenital birth defects in the children of residents in the high-noise areas near the airport. A similar study was conducted in the Metropolitan Atlanta area for the same 1970-1972 period, which found no differences in rates of birth defects that could be attributed to residence near the Atlanta airport (Edmonds et al., 1979). Because noise is known to be stressful, it would be desirable to conduct occupational studies involving women exposed to high levels of noise.

Exposure to Vibration

Based on the results of animal studies, it is presumed that vibration may affect the human embryo. There are no specific reports of adverse reproductive effects in the human female resulting from vibration. Without further study, it is not possible to draw any conclusions regarding the possible risks from situations that produce vibration to the human body.

ADVERSE EFFECTS OF WORKPLACE PHYSICAL FACTORS ON REPRODUCTIVE FUNCTION IN MEN

Exposure to Ionizing Radiation

Radiation sickness became recognized as an occupational disease after 1925. Since that time, very few cases have been reported in which gonadal effects in men were noted (Steeno and Pangkahila, 1984). There exists some indirect evidence, however, that occupational exposure to radiation affects male fertility. A questionnaire survey of Japanese radiological technicians exposed to more that 400 rads annually indicated that an abnormally high percentage were unable to have children (Steeno and Pangkahila, 1984). In a study involving 100 Bulgarian men occupationally exposed to x-rays, gamma rays and mild beta irradiation for at least 3 years (average, 8.81), there was a decreased sex drive and reduced sperm viability when compared to a control group of 100 healthy men (Steeno and Pangkahila, 1984). Neither of these studies provide dose information that would allow for quantitation of risk, nor do they control for other factors (occupational and nonoccupational) that can affect male fertility.

High doses of ionizing radiation clearly have an adverse effect on the gonads of men. The effects of relatively low doses (i.e., below 5-10 rad) are not well understood. Sperm production in men is suppressed by doses of x-irradiation as low as 15 rad (Clifton and Bremmer, 1983). Sperm production is transiently eliminated with doses of 50 rad. At very high dosages, in the range of 236-365 rad, severe damage occurs to spermatozoa that may persist for months (Council on Scientific Affairs, 1984). Significant return of sperm production can occur, even following dosages as high as 400 rad. Although numerous case reports exist concerning the testicular damage produced by radiation therapy for malignancies (Shalet, 1983), well-documented reports on the effects of occupational exposures, as indicated above, are limited.

Exposure to Nonionizing Radiation

The only form of nonionizing radiation that has been repeatedly associated with damage to male gonads is radiofrequency/microwave radiation. The available evidence is incomplete, however, with respect to dosage and influence of other variables. There is little doubt that radiofrequency/microwave radiation of sufficient intensity can damage the testes by thermal action. The possibility of athermal effects has not been adequately explored.

Most of the studies regarding occupational exposure to radiofrequency/microwave radiation involved military personnel. Clinical studies of radar operators in the U.S. Navy showed no adverse effect on male fertility. Sigler and coworkers (1965) reported a surprising finding that fathers of children with Down's syndrome gave more frequent histories of radar exposure during military service than fathers of normal children. A subsequent follow-up study, however, failed to confirm this finding (Michaelson, 1982). A clinical study of 31 men in Romania having long-term exposure (average 8 years) to microwaves indicated a prevalence of sexual disorders, which in most cases was accompanied by sperm abnormalities (Steeno and Pangkahila, 1984). Normal sperm production reportedly recovered in most of these men after removal from exposure for 3 months. A case report from the U.S. Air Force described a patient repeatedly exposed to high levels of microwave radiation (Steeno and Pangkahila, 1984). Damage to the testicular tissue was revealed by biopsy, and sperm abnormalities persisted for more than 1 year following cessation of exposure.

Recently, concern has arisen over the possible reproductive effects resulting from exposure of men to electric and magnetic fields associated with high voltage power lines. The available evidence in this area is not conclusive. A small cross-sectional study in Sweden was conducted on 53 workers having more than 5 years of exposure to 50 Hz electric fields from 400 kV substations (Knave et al., 1979). In comparison to 53 matched controls having no exposure, there were no significant health or fertility-related differences that could be attributed to employment at a substation. In a more extensive follow-up study, Nordstrom and coworkers (1983) administered questionnaires to 542 male employees or former employees at Swedish power companies whose electric field exposure was categorized into three subgroups: (1) less than 70 kV; (2) 130-200 kV; and (3) 400 kV. Occupational tasks were alvo divided into three subgroups: (1) working at high voltage switchyards; (2) construction or repair of switchyards and transmission lines; and (3) other tasks. An increased frequency of congenital malformations was indicated in the group where the father was a high voltage switchyard worker. On the other hand, there were no differences between the three subgroups of voltage exposure. Thus, it cannot be concluded that the incidence of congenital malformations is correlated with exposure intensity. In explaining their results, the authors pointed out that the size of the study may have been too small to allow for firm conclusions regarding risk.

Exposure to Radiation from Video Display Terminals

Studies on the emission of electromagentic radiation from VDTs at any frequency (x-ray, ultraviolet, visible, infrared, microwave, radiofrequency) have led to the conclusion that is is insufficient to cause adverse health effects (Council on Scientific Affairs, 1984). Specific studies on adverse reproductive effects in men exposed to VDT emissions have not been conducted, nor are any being planned.

Exposure to Gamma Irradiation in Food Processing

Expansion of the use of gamma irradiation (from cobalt-60 or cesium-137) and electron beams for food processing will undoubtedly place workers at increased risk of exposure to ionizing radiation. No information currently exists to indicate the potential magnitude of exposure to men engaged in various occupational tasks.

Exposure to Hyperbaric and Hypobaric Environments

Only limited data are available concering the influence of atmospheric pressure on male reproductive function. Donayre and coworkers (1968) described the semen characteristics of nine men exposed to high altitude (14,000 feet) in Peru for four weeks. A continuous decrease in sperm count was observed throughout the experiment. In addition, increased sperm abnormalities, decreased motility and decreased testosterone levels were associated with high altitude. The principal causative factor for these changes may have been hypoxia due to reduced ambient oxygen levels.

Exposure to Hot and Cold Environments

Hyperthermia is well-known for its antispermatogenic effect in humans. There are no reports available regarding the influence of cold environments on reproductive function in men. The greatest amount of documentation on the supression of spermatogenesis by heat is related to certain medical disorders, such as cryptorchidism (undescended testes), varicocele (enlarged veins in the scrotum) and acute febrile illness (Rock and Robinson, 1965). Case reports and epidemiologic studies on reproductive function in men working in hot environments are lacking. One group of experts has concluded that adverse reproductive effects in men from exposure to heat are unlikely to occur under normal working conditions (Council on Scientific Affairs, 1984). The opposite view has also been taken by at least one investigator who concluded that occupational exposure to heat may be a leading cause of male infertility (Medical World News, July 9, 1984). Further studies will be required to adequately address this issue.

Application of heat to the scrotum has been promoted as an effective, reversible means of male birth control. In controlled studies with human volunteers, elevation of testicular temperature by about 2.5-3.0°C for 30 minutes on several alternate days led to depression in sperm counts beginning at three weeks after exposure and lasting 3 to 5 weeks (Robinson et al., 1968; Rock and Robinson, 1965). Sperm counts were subsequently recovered and, in fact, increased beyond pre-exposure levels.

Exposure to Noise and Vibration

There is no evidence available that indicates that occupational exposure to noise is harmful to male reproductive function. Similarly, there is no conclusive evidence regarding adverse effects of vibration on reproductive function in men. One isolated report described sperm abnormalities and decreased fertility in professional drivers, which may have resulted from vibration (Council on Scientific Affairs, 1984). Other factors, however, including elevated intrascrotal temperature from prolonged sitting, might also be implicated.

ADVERSE EFFECTS OF PHYSICAL FACTORS ON LABORATORY ANIMAL REPRODUCTIVE FUNCTION

A. Female Reproductive Function

Ionizing Radiation

Numerous studies of ionizing radiation effects on ovaries, oocytes, and reproduction have been conducted in rodents, primates and many other species (Baker, 1971). The vast body of data from animal studies reveals wide variations in susceptibility according to species, age, germ cell stage and follicle size (Mandl, 1964; Baker and Neal, 1977). For example, extreme sensitivity of female germ cells to ionizing radiation is seen in postnatal mice and in prenatal squirrel monkeys. Oocytes in women and in adult rhesus monkeys, on the other hand, appear to be relatively resistant. In sensitive animals, such as the junvenile mouse, destruction of immature oocytes can result from dosages less than 6 rad.

In addition to effects on the ovary, ionizing radiation is an effective teratogenic agent. A great deal of radiation-induced teratogenesis research has been conducted with mice. In general, it has been concluded that the induction of birth defects by irradiation of the pregnant mouse increases in a linear fashion with increasing dose (Jacobsen, 1970). Moreover, there does not appear to be a threshold dose below which teratogenic effects cannot be demonstrated. Since the induction of birth defects by very low dosages of radiation (i.e., below 5 rad) would require large numbers of animals to obtain observable effects, it is unlikely that minimum effective doses could be experimentally demonstrated. It should be assumed, therefore, that in humans, as in animals, there is risk for birth defects associated with all radiation exposures, no matter how low the dose.

Nonionizing Radiation

The adverse effects of prenatal exposure to radiofrequency/microwave radiation at various frequencies has been extensively studied in rats, mice, chickens, Japanese quail, and insects. Studies have been concerned with morphologic alterations, as well as more subtle neurobehavioral changes. The power levels employed in many of these studies were sufficient to indicate that fetal malformations may have resulted from hyperthermia. At lower power densities, there appears to exist a minimum threshold level for induction of fetal abnormalities. Exposure of rats to a power density of 35 mW/cm^3 of 6000 MHz microwaves throughout pregnancy resulted in subtle long-term neurophysiologic alterations in the offspring (Jensh, 1984). Exposure of pregnant mice to 2.45 GHz continuous wave microwave radiation at a power level of 30 mW/cm^2 on gestation days 1-6 produced a decrease in implantation sites per litter and decreased fetal weight (Nawrot et al., 1981). Exposure to a power density of 30 mW/cm^2 on days 6-15 of gestation produced a slight increase in fetal malformations. No effects on the offspring were observed when pregnant mice were exposed to power densities of 5 and 21 mW/cm^2. Negative results have also been obtained with pregnant rats exposed to 915 MHz microwaves at a power level of 10 mW/cm^2 (Jensh et al., 1982), and with pregnant rats exposed to 100 MHz radiation (the frequency region of maximum human absorption) at a power density of 25 mW/cm^2 (Lary et al., 1983). These exposures produce no increase in maternal temperature. Thus, it appears that a threshold for induction of teratogenic effects in mice and rats by radiofrequency/microwave radiation may be in the power density region of about 30 mW/cm^2. These results also suggest that the 1982 ANSI exposure standard of 1 mW/cm^2 for frequencies between 30 and 300 MHz will provide adequate protection of pregnant women and the human fetus.

The teratogenic and embryotoxic effects of ultrasound have not been studied as extensively as with radiofrequency/microwave radiation. As with microwaves, when ultrasound exposure has been reported to induced fetal malformations, there is also an increase in maternal temperature (Kimmel et al., 1983). When pregnant mice were exposed to 1 MHz ultrasound at power densities up to 1.00 W/cm^2, no statistically significant effects on the fetus could be demonstrated (Kimmel et al., 1983). These results suggest that clinical applications of ultrasonic diagnostic procedures in pregnant women at typical power levels below 20 mW/cm^2 should not pose an unacceptable risk to the mother or fetus.

Information regarding the effects of low frequency electromagnetic radiation on reproduction in females is conflicting. Early studies with mice exposed continuously to 60 Hz electric fields (3.5 kV/m, 10 kV/m and 15 kV/m) over several generations indicated that mortality in the offspring may be higher in certain exposed groups (Marino et al., 1980). Fam (1980) reported no effects on fertility or development of offspring in mice exposed to a 240 kV/m, 60 Hz field for about three months. Similarly, in rats exposed for 30 days to a 100 kV/m, 60 Hz electric field, there was no effect seen on reproductive performance of the exposed animals, nor were any significant adverse effects noted in the offspring (Sikov, 1984).

Hot Environments

Artificially induced hyperthermia in rats and mice during gestation is reported to be embryolethal and teratogenic (Arora et al., 1979; Edwards, 1968; Lecyk, 1966). These studies are supported by numerous experiments with microwave-exposed pregnant animals where induced hyperthermia was shown to account for adverse effects on the fetus. Hyperthermia induced by elevated ambient temperature or by microwaves may not have equivalent effects on the fetus, however. Nawrot et al. (1981a) reported that in pregnant mice, increasing the deep body temperature by 2.3°C above normal with 2.45 GHz microwaves resulted in malformed fetuses; whereas, a similar rise in body temperature caused by elevated ambient temperature produced no increase in fetal effects.

Exposure to Noise

The most consistently reported reproductive effect of noise in animals is pregnancy rate reduction (Nawrot et al., 1981b). In addition, there is evidence that embryolethality and fetolethality are increased by noise exposure. Both positive and negative findings with respect to teratogenesis have been reported. Differences in noise level, and variations in spectral and temporal patterns of exposure may all be expected to influence the biologic effect produced. Thus far, it has not been possible to use the results from the available animals studies to predict whether similar effects may occur in humans.

Atmospheric Pressure

There is little information available regarding the effects of atmospheric pressure variations on female reproduction. Several studies have been conducted in pregnant dogs and sheep using conditions designed to simulate underwater diving and rapid decompression (Nemiroff et al., 1981; Stock et al., 1980). In general, it appears that in the late stages of fetal development, the fetus appears to be less susceptible to decompression sickness than the mother. These studies do not provide an indication of the possible effects of hyperbaric exposures on the embryo and fetus early in pregnancy.

Vibration

There is insufficient data available from animal studies to critically evaluate the reproductive effects of mechanical vibration. Bantle (1971) exposed pregnant mice at 4 1/4 and 7 days gestation to whole body vibration for 10 minutes at three different frequencies (5Hz, 10 Hz, 20 Hz). Mouse embryos were found to be quite resistant to vibration, although in the 4 1/4 day embryos, the incidence of abnormalities was increased in the 20 Hz group.

B. Male Reproductive Function

Ionizing Radiation

Testicular x-irradiation and gamma irradiation in animals exerts profound effects on developing sperm. Numerous studies have been conducted in mice to assess dose-reponse relationships for induction of sperm abnormalities (Bruce et al., 1974; Oakberg, 1959). Using mice exposed to testicular x-irradiation, Young et al. (1982) determined that the dose to produce a doubling in the number of abnormal sperm in comparison to controls was 39 rad. Clifton and Bremmer (1983) determined that the dose of x-irradiation to produce a 50% suppression of type A spermatogonia was 30.0 rad for the mouse and 917 rad for the human. This indicates that human type A spermatogonia are about 3.1 times more sensitive to ionizing radiation than those of the mouse. In addition to testicular damage, irradiation of the testis has a mutagenic effect on male germ cells, as evidenced by reduction in post-implantation survival after exposed males are mated with females (Saunders et al., 1983).

Nonionizing Radiation

Numerous studies have been conducted on testicular and reproductive function in rats and mice exposed to radiofrequency/microwave radiation. Testicular degeneration is clearly associated with microwave dosages sufficient to cause tissue heating (Council on Scientific Affairs, 1984; Lebovitz and Johnson, 1983; Saunders and Kowalczuk, 1981). At a dosage of microwave radiation (1.3 GHz) sufficient to cause a net change in body temperature of 1.5°C, no effects were seen on the testes of rats (Lebovitz and Johnson, 1983). In contrast with the effects of ionizing radiation, evidence concerning a mutagenic effect for microwave radiation is inconsistent and conflicting (Saunders et al. 1983). On the other hand, impaired male fertility as evidenced by a reduced pregnancy rate in mated females can be achieved with sufficient dosages of microwaves (Kowalczuk et al., 1984). The extent to which thermal effects account for these results is not clearly established.

Atmospheric Pressure

From the limited data available, it appears that male fertility can be suppressed by both hypobaric and hyperbaric environments. Donayre et al. (1968) cited studies where brief exposure to high altitude causes impaired spermatogenesis, destruction of germinal epithelium and testicular atrophy in several species of animals. These changes are apparently reversible upon descent to sea level.

Baden and coworkers (1982) exposed mice to high pressure (50 ATA) at intervals throughout one spermatogenic cycle which were then mated with untreated females in order to evaluate effects on sex drive and fertility. A significant effect on male fertility resulted, as evidenced by reduced pregnancy rates in the mated females. In addition, there was a reduction in the live litter size, although no indication of teratogenic effects was obtained. The precise mechanism for the action of high pressure on male fertility could not be identified; especially in view of the fact that gross morphological abnormalities in the sperm were not seen.

SUMMARY OF WORKPLACE PHYSICAL HAZARDS TO REPRODUCTION IN WOMEN AND MEN

Human exposure to physical forces occurs in virtually all occupational settings. Many of these forces are naturally-occurring factors of our environment which, in certain occupations, are magnified due to manmade sources such as heavy machinery, electrically powered equipment, and other devices for energy conversion. Widely recognized physical forces in the workplace include ionizing radiation, optical radiation, radiofrequency/microwave radiation, electric and magnetic fields, atmospheric pressure, hot or cold environments, noise, and vibration. Physical forces, alone and in combination, are probably the most prevalent of all occupational hazards.

Certain health effects resulting from occupational exposure to physical forces, such as noise-induced hearing loss, heat stress, and vibration-induced numbness, have been recognized for many decades. On the other hand, the evidence for adverse effects on reproduction from occupational exposure to physical forces is in most cases either inferential or nonexistant. This lack of information, however, should be viewed in light of the fact that very few well-documented studies have been conducted for the specific purpose of evaluating reproductive hazards resulting from exposure to physical forces in the workplace.

In women, there is conclusive evidence from nonoccupational studies that exposure to ionizing radiation (e.g., medical use of x-rays) is harmful to the ovaries and to the fetus. This evidence is supported by the results of studies with experimental animals. There are no reports, however, of adverse reproductive effects in women occupationally exposed to ionizing radiation.

Suggestive evidence of human teratogenicity or other harm to female reproduction is available for nonoccupational exposures to heat (hot tubs and saunas), hyperbaric environments (scuba diving), hypobaric environments (residence at high altitudes), and noise (residence near an airport). Because of limitations in population size and extent of data collection, these suggestive studies will require subsequent confirmation before the results can be accepted. Furthermore, there is no conclusive evidence from women exposed to these forces in occupational settings to support the existence of similar reproductive risks in the workplace. Physical forces for which there is no clear evidence for harm to human female reproduction either in occupational or nonoccupational environments include optical radiation (ultraviolet, visible, infrared, laser), ultrasound, radiofrequency/microwave radiation, radiation associated with video display terminals (VDTs), electric and magnetic fields, cold, vibration, gravity changes, and acceleration.

Documentation of harmful effects on male reproductive function due to physical forces in the workplace is very limited. Some evidence is available linking occupational exposure to ionizing radiation (radiological technicians) and microwaves (military personnel) with sperm abnormalities and decreased fertility. These effects do not appear to be permanent. The harmful effects of ionizing radiation on male workers is supported by numerous studies on the effects of nonoccupational exposure to x-rays. The available data indicate that the severity of damage to the male reproductive process increases in proportion to the dose of ionizing radiation received. Suggestive evidence of an occupational reproductive hazard for men exists for hot environments, which is supported by studies of nonoccupational hyperthermia in men. In addition, there are reports that hypobaric environments (i.e., residence at high altitudes) adversely affect sperm and semen characteristics, although no such reports are available from occupational settings. Among the physical forces where there is no clear evidence for adverse effects on male reproductive function, in either occupational or nonoccupational settings, the most important are optical radiation, electric and magnetic fields, hyperbaric environments, cold environments, noise, vibration, gravity changes, and acceleration.

The results of studies with experimental animals exposed to various physical forces tend to support and extend the observations made in exposed human populations. Harmful effects on the fetus have been noted in pregnant animals exposed to ionizing radiation, high doses of microwave radiation (i.e., above a power density of about 30 mW/cm^2), hyperthermia (i.e., by elevated ambient temperature or by microwaves), and noise. In male animals, antifertility and antispermatogenic effects are associated with exposure to ionizing radiation, microwave radiation (particularly at doses causing tissue heating), and hyperbaric environments. Significant information gaps concerning harmful effects of physical forces on the reproductive process are addressed below under Research Needs.

RESEARCH NEEDS

There is an obvious need for a wide range of studies on physical factors influencing reproduction. Research needs range from basic mechanistic studies at the molecular level to epidemiologic investigations aimed at identifying and quantifying risks under real world conditions of exposure. Many of the research concerns regarding the evaluation of reproductive hazards in general were recently addressed by the Interagency Regulatory Liaison Group (IRLG) Reproductive Toxicity Risk Assessment Task Group (Infante and Tsongas, 1983). At this workshop, the major questions affecting reproductive risk assessment were raised, such as:

1) Which animal and human endpoints are useful for human reproductive risk assessment?
2) Which procedures can be used for qualitative and/or quantitative risk assessment of potential human reproductive hazards with available evidence?
3) How can information on mechanism be used for interpretation of experimental data and risk assessment?

These questions are all relevant to the investigation of physical factors. In addition, for many of the physical factors of concern with respect to reproductive hazard potential, specific information gaps exist.

Factors responsible for lower human birth rates at high altitudes are not clear. It is believed that reduced ambient oxygen levels acting upon the mother or father, or both, may explain the effects observed. More research is needed to explore the possibility that high altitudes may not only reduce fertility, but may also lead to teratogenic effects on the developing embryo, or gene mutations in the sperm. Increased ambient pressure seems to adversely affect the fetus in women and animals, although more studies are required to establish the nature and extent of risks involved. There are no reports available concerning the effects of increased pressure on human male reproductive function, or on the ovaries and endocrine system of females.

It has been suggested that there is no clear theoretical basis to expect that electric and magnetic fields associated with 60 Hz power lines cause adverse reproductive effects (Council on Scientific Affairs, 1984). Nevertheless, suggestive evidence exists from human and animal studies to raise concern in this area. Furthermore, it is apparent that low frequency electromagnetic fields interact with biological systems at the cellular and subcellular level (Dodge, 1984). Further research is needed to relate these molecular interactions to possible reproductive hazards. Additional epidemiologic studies of exposed worker populations may help to clarify and identify any real risks.

The possible adverse effects on reproduction due to gravity changes and/or acceleration are virtually unknown. The increased exposure of men and women to weightlessness and high gravitational forces during space flight indicates a need for studies in this area.

Although hyperthermia is known to adversely affect spermatogenesis in men, there is a surprising lack of studies involving men occupationally exposed to hot environments. Retrospective and prospective epidemiologic studies in this area are needed. In addition, studies in female animals suggest that maternal hyperthermia adversely affects the embryo and fetus. Studies of human females exposed to hot environments are lacking, both with respect to effects during pregnancy and to effects on fertility and the ovaries. Essentially nothing is known regarding the effects on human reproduction from exposure to cold environments. Epidemiologic studies could provide useful information concerning reproductive hazards in men and women associated with hypothermia.

The widespread occurrence of high noise levels in the workplace raises concern over health effects other than hearing loss. There exists only suggestive evidence that human exposure to noise can adversely affect reproduction. Retrospective and prospective epidemiologic studies of men and women exposed to measured noise levels would be extremely useful in identifying possible reproductive hazards.

Optical radiation in the form of ultraviolet, visible and infrared radiation is not believed to cause adverse reproductive effects. Recent reports of adverse reproductive outcome associated with the use of VDTs, however, has stimulated research in this area. Since epidemiologic studies are currently in progress with respect to VDT work, this issue should be clarified in the near future. Further speculation on the adverse reproductive effects of optical radiation is probably not warranted at this time.

Considerable controversy surrounds the issue of the reproductive hazards of radiofrequency/microwave radiation. There appears to be some basis for the conclusion that reduced fertility in men can result from exposures of sufficient intensity. It is not clear, however, whether there is a nonthermal component to the testicular damage produced by microwaves. Further animal research and epidemiologic studies will be required in this area. There is very little information from either animal studies or epidemiologic investigations to evaluate whether reproduction in females is adversely affected by workplace exposure to radiofrequency/microwave radiation. This area also requires exploration.

There are no conclusive studies regarding reproductive hazards to men or women exposed to whole body vibration. Supporting evidence from animal studies is also lacking. Although it is believed that the fetus is relatively protected from the effects of vibration, this contention needs to be confirmed. Additional information would also be useful concerning the specific effects of vibration on the ovary and testis.

At the basis of all future research on reproductive effects of physical factors should be the evaluation of long-term consequences of low-level exposures. Animal studies involving exposure to maximum tolerated doses, and human studies of populations exposed to doses beyond currently accepted limits, will be especially helpful in assessing risk. These will be critical in the performance of high-to-low-dose extrapolation involving levels that are likely to be encountered in the workplace. Further research into more sensitive endpoints, possibly at the cellular or molecular level, would also provide a valuable tool for predicting where hazardous situations may arise.

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EFFECT OF WORKPLACE CHEMICALS ON REPRODUCTIVE FUNCTION IN LABORATORY ANIMALS

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I. INTRODUCTION

Numerous agents have been shown to adversely affect the reproductive process in animal test systems. Some foreign chemicals affect reproduction by inhibition of fertility in the male or female, while others are classified as developmental toxicants. Developmental toxicity can be expressed up to the time of puberty and may be manifested as: (1) death of the embryo or fetus (embryolethality); (2) structural malformations (teratogenicity); (3) altered growth of the body or certain organs (fetotoxicity); and (4) functional deficits of the organism (e.g., neurobehavioral disturbances) or in certain organ systems.

Standard protocols are not commonly followed for evaluating chemical effects on fertility. In male animals exposed to foreign agents, reported changes may include effects on testicular weight or histology, reduction in sperm count and abnormally formed sperm, and complete arrest of spermatogenesis. In female animals, changes in the estrus cycle or failure to conceive may be reported. Interruption of pregnancy due to embryonic or fetal death can also result from a chemically-induced dominant lethal mutation transmitted via the germ cells of the father. Although chemical effects on male fertility have often been studied in animals, very little research has been conducted on fertility in females exposed to environmental chemicals.

Protocols for assessing developmental toxicity have become relatively standardized. A typical assay involves the administration of a test substance to pregnant animals (typically mice, rats, or rabbits) during the gestational period when most of the major organs in the fetus are being formed. Observations are made of maternal responses throughout pregnancy, and the fetuses are examined just prior to term. The relationship between maternal toxicity and developmental toxicity to the fetus is especially important to evaluate, because it can define doses that harm the fetus without causing any observable effects on the mother. An agent that produces developmental toxicity at a dose that is minimally toxic or nontoxic to the maternal animal is regarded to be selectively toxic to the fetus. Among the various manifestations of developmental toxicity, functional deficiencies are the least studied and, hence, the most poorly understood in terms of risks from foreign chemicals.

The results of reproductive toxicity studies with animals are generally supportive of effects reported in male and female workers exposed to the same substance. In most cases, it has been much easier to demonstrate a causal relationship between exposure to a specific chemical and adverse reproductive effects in animals than it has been in humans. This success can be largely attributed to the strict controls and more detailed analyses that laboratory animal studies allow in comparison to the complexities of the real world workplace environment and varied human lifestyles. Thus, it is believed that animal models for chemical effects on reproduction have good predictive value for humans. For the numerous chemicals reported to affect reproduction in animal studies but with no confirming human evidence, the predictive value of the animal models remains to be established.

Much of the relevant literature published up to 1982 regarding reproductive toxicity testing in animals was reviewed by Barlow and Sullivan (1982). Their findings along with more recent reports of animal experiments are summarized below.

II. METALS

A. Lead

Inorganic lead (metallic lead) and lead compounds (lead salts, lead oxides) are well known for their adverse effects on animal reproduction. When administered orally, by inhalation, or by injection during pregnancy lead produces maternal toxicity, fetotoxicity and developmental toxicity in the newborn. Lead may also inhibit fertility in female animals by causing failure of the fertilized ovum to implant in the uterus (Wide, 1983). Perhaps the most significant effect seen in animals exposed to inorganic lead is delayed development of the brain in newborns.

Administration of daily intramuscular injections of lead acetate at a dose of 5 mg/kg body weight during pregnancy induced abortions and death in monkeys (Tachon et al., 1983). At a lower dose of 1 mg/kg body weight/day, kidney damage developed in mothers and erythrodiapedesis (leakage of red blood cells through the walls of the blood vessels) was observed in the brains of the newborns at birth. Development of the brain of newborn rats is delayed by administration of low levels of lead in the pregnant mother's drinking water (200 mg/ℓ of drinking water) during the period of gestation (Bull et al., 1983; McCauley et al., 1982). Delayed development of the cerebral cortex in rat pups was correlated with delays in the development of exploratory and locomotor activity, and impaired learning. When pregnant rats were given high levels of inorganic lead in their drinking water (1000-4000 mg/ℓ) the size and number of litters were reduced, and the offspring showed dose-related decreases in brain weight, body weight, and body length (Carmichael et al., 1981).

The reproductive toxicity of inorganic lead in male animals is not as well understood as in females. Adverse effects have been noted on spermatogenesis and the male gonads, although differences in degree of response occur, presumably due to differences in dose, duration and method of exposure, species, and experimental design (Thomas and Brogan, 1983). In some cases, no effect of inorganic lead can be shown on the male reproductive system. Male rabbits injected three times weekly for 14 weeks with 0.25 mg or 50 mg lead acetate displayed no effect on the sperm count, sperm morphology, or histopathology of the testes (Williams et al., 1982). Moreover, the number of sister chromatid exchanges in lymphocytes or the number of mironuclei in bone marrow erythrocytes were not affected by the treatment; implying no mutagenic effect was produced.

Organic lead compounds, such as tetraethyl lead and tetramethyl lead, do not appear to be associated with inhibition of fertility or developmental toxicity in animals. Embryolethal and fetotoxic effects can only be produced at doses of organic lead which are severely toxic to the mother (Barlow and Sullivan, 1982). Teratogenic effects are not seen, even at doses which produce maternal toxicity. In male rats given tetraethyl lead, no dominant lethal mutations were transmitted to the offspring when the treated males were mated with untreated females (Barlow and Sullivan, 1982).

B. Mercury

Both organic and inorganic mercury compounds have been studied for reproductive toxicity in animal models. All forms of mercury are capable of crossing the placenta, although the placental transfer of organic mercury compounds is more efficient than for inorganic mercury (Barlow and Sullivan, 1982). In male mice a single injected dose of 1 mg mercury/kg of body weight resulted in temporary infertility, but no transmission of dominant lethal mutations (Barlow and Sullivan, 1982). The antifertility effect of organic mercury was more pronounced than for inorganic mercury. In female mice, low doses of inorganic mercury (0.1 mg/day for 8 days) caused a transient failure of the estrus period; in female hamsters a daily injection of 1 mg inorganic mercury for 2-4 days also caused absence of ovulation.

Inhalation of metallic mercury vapor (0.3 ppm in air) and injection of inorganic mercury compounds (2-4 mg, single dose) in pregnant rodents causes embryolethal, fetotoxic and teratogenic effects (Barlow and Sullivan, 1982). In addition, exposure of female rats to 0.3 ppm mercury vapor increased the length of the estrus cycle, possibly by an action at the hypothalamic and/or pituitary level. Minimum dose levels for the production of developmental toxic effects by inorganic mercury have not been established.

C. Cadmium

The capability for cadmium to produce severe testicular damage has been well documented in male mice, rats, hamsters, rabbits, guinea pigs, dogs and squirrels (Barlow and Sullivan, 1982). Irreversible testicular damage, which follows injection of cadmium salts or chronic oral dosing, is believed to result from destruction of the delicate blood vessels in the testes. Fertility in male rodents can be inhibited by a single injection of cadmium at 1 mg/kg of body weight, or a single oral dose of 100 mg/kg of body weight. Fertility can be impaired at cadmium doses which do not cause histological damage to the testes. Although cadmium is destructive to the testes of rodents, dominant lethal mutations are not produced.

Doses of cadmium which are harmful to male reproduction do not seem to impair fertility in female animals. When administered during pregnancy, however, cadmium is embryolethal, fetotoxic, and teratogenic in all species tested. At comparable doses, effects on the fetus are more severe when cadmium is given to the mother by injection rather than by oral administration. This difference is due to relatively poor oral absorption of cadmium. Anemia in the fetus and the newborn, as well as in the dam, is a prominent effect resulting from cadmium exposure during pregnancy. In addition, cadmium produces abnormal calcium metabolism in the fetus which results in skeletal malformations and brittle bones. The succession from fetotoxicity to teratogenicity to intrauterine death of the fetus occurs over a very narrow dose range.

D. Arsenic

Inorganic arsenic in the pentavalent (arsenate) or trivalent (arsenite) form is fetotoxic and teratogenic to rodents (Hood and Vedel-Macrander, 1984; Hood and Harrison, 1982; Hood et al., 1982; Morrissey and Mottet, 1983). Arsenate has been more extensively studied than arsenite, and at doses equally toxic to the mother arsenate is capable of producing a higher malformation rate than arsenite compounds. On the other hand, arsenite is more toxic than arsenate, and hence is teratogenic at lower doses. The inorganic arsenicals produce a broad spectrum of developmental toxic effects ranging from inhibition of fetal growth and prenatal death to gross and skeletal malformation, including neural tube defects such as exencephaly (brain outside of the cranial cavity). A single intraperitoneal injection of sodium arsenate at 45 mg/kg body weight to pregnant mice on day 8 of gestation has resulted in a 65% incidence of exencephaly (Morrissey and Mottet, 1983). Higher doses (60 or 75 mg/kg body weight) produced significant maternal toxicity. Oral treatment with sodium arsenate and sodium arsenite is considerably less toxic and teratogenic than treatment given by intraperitoneal injection. In the case of arsenite, doses required to produce fetotoxicity and maternal toxicity are similar. Organoarsenicals (e.g., methylated arsenicals such as sodium cacodylate) are significantly less toxic to the rodent embryo than are inorganic arsenic compounds (Hood et al., 1982).

Arsenic does not appear to have a significant effect on fertility in animals of either sex (Barlow andSullivan, 1982). In male animals, arsenic does not produce a dominant lethal effect, although it may potentiate the action of other mutagens.

E. Boron

In studies with rats and dogs, boron was shown to exert specific toxic effects on the male gonads (Beyer et al., 1983). Sodium borate and boric acid when given orally (1170 ppm of boron in the diet) to rats, for up to two years caused testicular atrophy and sterility. Similar effects were shown with dogs given

1170 ppm of boron in the diet for 38 weeks. No effects in dogs or rats were reported when the animals were given 350 ppm of boron in the diet. One study in rats, however, indicated that sperm count and mobility were adversely affected at boron doses (given in drinking water) of 0.3 mg/kg body weight/day for six months. A 3-generation reproduction study was conducted in male and female rats fed diets containing 117, 350, and 1170 ppm boron equivalents of sodium borate (≃103.5, 309.7, and 1035.4 mg/kg/day) and boric acid (≃66.9, 200, and 668.6 mg/kg/day). At the highest dose level both male and female rats were sterile; the males had reduced sperm counts, and there was decreased ovulation in females. Reproduction was not affected at the two lower concentrations of boron in the diet.

The only teratogenic studies available for boron involved the effects of boric acid on chick embryos (Beyer et al., 1983). Injection of boric acid into chicken eggs caused growth inhibition, interference with feather growth, and several types of malformations. The relevance of these results to humans is not established.

F. Manganese

Manganese is an essential element in mammals, and therefore readily crosses the placenta and reaches the fetus. Preferential accumulation of manganese occurs in the brain and spinal cord of the fetus (Lyden et al., 1983; Barlow and Sullivan, 1982). In adult male rodents manganese appears to have a selective toxic effects on the testes and accessory sex organs at otherwise non-toxic doses. Testicular damage was produced by oral and parenteral (intraperitoneal, intravenous) administration of manganese compounds to rats or mice, and by intratracheal instillation of manganese dioxide in rabbits. The effect of manganese on fertility in males was only documented in rabbits. A single intratracheal instillation of manganese dioxide at a dose of 250 mg/kg of body weight resulted in extensive degeneration of the semineferous tubules eight months after the treatment. The male rabbits were sterile when paired with fertile females.

In female rodents, manganese did not impair fertility or produce teratogenic effects. Female rats maintained on a diet containing up to 1000 ppm manganese from weaning to sexual maturity did not exhibit reduced fertility or increased abnormalities in their offspring when mated to untreated males (Barlow and Sullivan, 1982). Additional studies with pregnant mice, hamsters and rabbits indicated that manganese was not teratogenic at doses which did not produce maternal toxicity. Postnatal development of rodents, however, may be adversely affected if manganese is tranfered from the mother to the newborns during suckling (Lown et al., 1984; Barlow and Sullivan, 1982). Accumulation of manganese in the brain of the newborns may account for biochemical disturbances in the brain as well as poor weight gain and postnatal survival.

III. Agricultural Chemicals

A. Dibromochloropropane (DBCP)

DBCP is selectively toxic to the gonads of male rats, rabbits, guinea pigs and monkeys (Whorton and Foliart, 1983; Barlow and Sullivan, 1982). In male rats testicular weight was reduced to 50% of normal by inhalation of 5 ppm DBCP in air for 70 days, and fertility was impaired by chronic oral administration of DBCP at 0.5 mg/kg body weight/day. In the male rabbit, sperm counts were decreased by inhalation exposure to DBCP at 1 ppm in air. At higher exposure levels in the rat and rabbit, DBCP produced severe degeneration of the testes, complete arrest of spermatogenesis, and other signs of general toxicity to the kidneys and liver. A dominant lethal effect (increased incidence of fetal resorption) was indicated for male rats exposed to 10 ppm DBCP by inhalation for up to 14 weeks. This effects was reversible upon removal of male rats from DBCP exposure.

Effects of DBCP on female animals are not as well studied as in males. Chronic oral administration of DBCP (10 mg/kg/day) to female rats caused prolongation or cessation of the estrus cycle, with evidence of abnormal cycling appearing within one month from the start of exposure. Oral administration of DBCP at a dose of 5 mg/kg body weight/day for 10 weeks to female rats producéd a slight decrease in fertility when the treated females were subsequently mated with untreated males. DBCP does not appear to be teratogenic in the rat. The only adverse effect of DBCP on pregnancy was reduction in fetal weight gain at high doses (50 mg/kg/day on days 6-15 of pregnancy), which was probably secondary to maternal tox- icity (Barlow and Sullivan, 1982).

B. DDT [2,2-bis(p-chlorophenyl)1,1,1-trichloroethane]

DDT (p,p'-DDT; o,p'-DDT; technical DDT) has been studied for reproductive effects by oral administration to the rat, mouse, rabbit and dog (Council on Environmental Quality, 1981). Several extensive multigeneration studies have been conducted with DDT. At dietary concentrations above 7 ppm, chronic exposure to DDT has produced impaired fertility in female rats and poor weight gain and survival of the offspring. In the dog, chronic oral administration of technical grade DDT at 1, 5, or 10 mg/kg body weight/day for 3 generations was associated with earlier onset of estrus in females, but other parameters of reproduction were normal. At 12 mg/kg body weight/day for 14 months, diminished libido was reported in males and delayed estrus, infertility, and increased infant and maternal mortality was reported in female dogs.

Administration of DDT to rodents during pregnancy is not generally associated with the production of gross teratogenic effects. The available evidence indicates, however, that DDT exposure during pregnancy may lead to functional disturbances in the offspring during the postnatal period. Functional deficits that have been reported in mice include delayed acquisition of conditioned avoidance responses and decreased aggressive behavior in male offspring. In pregnant rabbits, oral administration of p,p'-DDT at 50 mg/kg body weight on days 7, 8 and 9 of gestation produced premature delivery, increased fetal resorptions (death), and decreased intrauterine growth, but no congenital malformations.

C. Kepone (Chlordecone)

In male rats testicular atrophy in the absence of other toxic effects was produced by chronic dietary administration of kepone at 10 ppm (Barlow and Sullivan, 1982). At higher levels in the diet (30-40 ppm) kepone causes some reduction of male fertility in mice and rats, as evidenced by reduced litter size. In female rats and mice, dietary levels of kepone at 30 ppm and above caused persistent estrus and failure to ovulate. Although doses of kepone as low as 10 ppm did not affect the estrus cycle or ovulation, fertility in female mice was reduced in terms of number of litters produced, litter size, and increased time to mating. When both male and female mice were exposed to kepone in the diet, fertility was reduced at a dietary concentration of 5 ppm.

When kepone was given to pregnant rats and mice, fetotoxicity and teratogenicity were only seen at doses (10-12 mg/kg/day) that were toxic to the mother. Functional disturbances during postnatal development, however, may result from gestational and perinatal (shortly before or after birth) exposure to kepone. Female offspring are particularly susceptible to kepone exposure during the perinatal period, which causes abnormal development of sexual function. In addition, neurobehavioral development in the rat is impaired by gestational and perinatal exposure to kepone, presumably due to a direct effect on the developing brain (Squibb and Tilson, 1982; Rosecrans et al., 1982; Hong and Ali, 1982; Seth et al., 1981).

D. Carbaryl

When administered at high doses carbaryl has caused several types of adverse reproductive effects in laboratory animals. Carbaryl was fed to rats and gerbils at a level of 2000, 5000 or 10,000 ppm in the diet over a period of three generations (Collins et al. 1971). At the highest dose level reproductive failure was observed in female animals. At lower dose levels evidence of reduced fertility, reduced litter size and decreased viability of the offspring was obtained. When carbaryl was given to pregnant rhesus monkeys at daily doses up to 10 mg/kg of body weight during gestation, no effect was seen on the incidence of abortion or stillbirth (Dougherty and Coulston, 1975). It is known, however, that carbaryl can cross the placenta in pregnant rats and mice and enter the fetus (Courtney et al. 1983). Administration of carbaryl in a single dose to male mice had no effect on sperm morphology, sperm counts or testicular weight (Osterlok et al. 1983).

When administered orally during gestation, carbaryl was teratogenic to rabbits, guinea pigs, beagle dogs, and miniature swine, but not to mice, rats, hamsters or monkeys (Lechner and Abdel-Rahman, 1984; Murray et al., 1979; Robens, 1969; Weil et al., 1973; Smalley et al., 1968; Earl et al., 1973; Benson et al., 1967; Coulston, 1971; Dougherty and Coulston. 1975). The weight of evidence from these studies indicates that a significant increase in teratogenic effects does not seem to occur in the absence of maternal toxicity.

Beagle dogs and miniature swine appeared to be the species most sensitive to the reproductive effects of carbaryl. In these species fetotoxicity, embryolethality and teratogenicity were demonstrated with dietary administration of carbaryl during pregnancy at dose levels ranging from 3-50 mg/kg body weight per day. Maternal effects associated with carbaryl exposure during pregnancy included difficult births, decreased fertility and placental separation.

E. 2,4-Dichlorophenoxyacetic acid (2,4-D)

The reproductive effects of 2,4-D and several of its ester derivatives have been rather extensively studied in rats and mice. The evidence for teratogenic effects is limited and, in general, where fetal malformations have been observed they were accompanied by signs of maternal toxicity (Courtney, 1977; Khera and McKinley, 1972; Schwetz et al., 1971; Unger et al., 1981; Collins and Williams, 1971). Significant increases in fetotoxic effects have been observed in the absence of apparent maternal toxicity. These fetotoxic effects were typically decreased fetal weight and delayed bone ossification.

The effects of long-term exposure to 2,4-D on reproduction were investigated in a three-generation study using rats (Hansen et al., 1971). Animals received 2,4-D in the diet at 100, 500 or 1500 ppm (corresponding to 5-75 mg/kg body weight per day) for two years. At the highest exposure level mortality in the newborns was increased along with significant loss in weight among nursing offspring. There was no effect on parental fertility or litter size at the 1500 ppm exposure level. At the 100 and 500 ppm exposure levels, no effects were seen on fertility, litter size or viability of the offspring during the first 21 days of life.

F. 2,4,5-Trichlorophenoxyacetic Acid (2,4,5-T)

Teratogenic effects resulting from exposure to 2,4,5-T have been well-documented in rodents. In particular, several studies have established that purified 2,4,5-T (i.e. not contaminated with 2,3,7,8-TCDD; see Section G below) induces cleft palates in mice (Courtney et al., 1970a,b; Neubert and Dillmann, 1972; Roll, 1971; Courtney, 1977; Gainer et al., 1975). Oral doses of 2,4,5-T producing a significant increase in cleft palates in mice have been as low as 25 mg/kg of body weight given during gestation. Teratogenic effects were seen in the absence of apparent maternal toxicity.

Rats appear to be less sensitive than mice to the teratogenic effects of 2,4,5-T. Oral doses during gestation of 100 mg/kg of body weight and higher have caused maternal toxicity, fetotoxicity and skeletal abnormalities (Sokolik, 1973; Khera and McKinley, 1972; Khera et al., 1971; Sparaschu et al., 1971; Emerson et al., 1970, 1971). A dose of 2,4,5-T at 25 mg/kg of body weight given daily during gestation appeared to have no effect on the outcome of pregnancy in rats. A three-generation reproduction study was conducted with rats exposed to 2,4,5-T in the diet resulting in a dose of 3, 10 or 30 mg/kg of body weight per day (Smith et al., 1981). At the highest exposure level, survival of the newborns was decreased but no other effects on reproduction were observed.

In addition to rats and mice, the reproductive effects of 2,4,5-T have been studied in hamsters, rabbits, lambs and monkeys. A wide range of abnormalities and decreased viability of offspring was reported for hamsters (Collins and Williams, 1971), although results with rabbits, lambs and monkeys were essentially negative for teratogenicity (Emerson et al., 1972; Thompson et al., 1971; Binns and Balls, 1971; Dougherty et al., 1973, 1975; Wilson, 1971).

G. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD)

Early studies with 2,4,5-T contaminated with 2,3,7,8-TCDD (Courtney et al., 1970 a,b) indicated that teratogenic effects were produced in mice. Subsequent studies focused on the reproductive effects of pure 2,3,7,8-TCDD. Cleft palate, kidney malformations and other types of abnormalities have been observed in the offspring of mice exposed to 2,3,7,8-TCDD during pregnancy (studies reviewed in U.S. EPA, 1984). With a minimum effective dose for induction of teratogenic effects at 1 μg/kg of body weight per day, 2,3,7,8-TCDD represents the most potent teratogen known.

The teratogenic effects of 2,3,7,8-TCDD in mice are supported by the results of investigations with rats (U.S. EPA, 1984). 2,3,7,8-TCDD produced teratogenic and fetotoxic effects in all rat strains tested. The reproductive effects of 2,3,7,8-TCDD were also studied in a three-generation study using rats exposed to diets providing doses of 0.001., 0.01 or 0.1 μg/kg of body weight per day. At the high and intermediate dose levels, significantly impaired fertility and decreased neonatal survival resulted. At the lowest dose tested (0.001 μg/kg/day) a significant increase in kidney malformations was seen in the first generation of newborns from rats exposed to 2,3,7,8-TCDD, but not in subsequent generations.

Several studies have been conducted with monkeys exposed to 2,3,7,8-TCDD showing that reproduction and pregnancy outcome are adversely affected (U.S. EPA, 1984). Failure to conceive, abortion, and stillbirth resulted from exposure either before or during pregnancy. The minimum dose required to adversely affect reproduction in monkeys has not been determined; effects have been observed with exposures to 2,3,7,8-TCDD for 7 months of about 0.0015 μg/kg of body weight per day.

IV Polyhalogenated Biphenyls

B Polybrominated Biphenyls (PBB)

Developing fetal and newborn animals are readily exposed to PBB by transplacental and milk transfer from the exposed mother (Ecobichon et al., 1983; Barlow and Sullivan, 1982). Placental transfer of PBB has been shown in the cow, rat and guinea pig.

Adverse effects of PBB on fertility in mature animals appears to be associated with doses that produce other toxic symptoms as well. Testicular atrophy and reduced or abnormal sperm have been demonstrated in bulls given PBB-contaminated diets. In female rhesus monkeys given 0.3 ppm PBB in the diet for seven months, menstrual cycles were lengthened in four of seven treated animals, although fertility was apparently not impaired.

In pregnant rodents given PBB during gestation fetotoxic effects, primarily reduced fetal weight, were seen at relatively high levels of exposure (1000 ppm in the diet corresponding to about 50 mg/kg/day). Teratogenic effects in rats were produced with very high single PBB doses of 400 mg/kg body weight and above. These teratogenic effects may be solely associated with maternal toxicity, although this is not clear.

One study has described adverse effects on pregnancy in rhesus monkeys chronically maintained on a diet containing 0.3 ppm of PBB before breeding and during pregnancy and lactation. All seven of the treated monkeys become pregnant, but only five delivered live offspring. The five infants born alive appeared normal but had low birth weights. In addition, the postnatal weight gain up to 16 weeks of age was depressed in infants from PBB-exposed mothers.

Polychlorinated Biphenyls (PCB)

The reproductive effects of commercial PCB mixtures and individual PCB isomers have been rather extensively studied in rodents and primates. Because passage of PCB into the milk fat is a major route of excretion in nursing animals, concern has been expressed for the effects of PCB on offspring both prenatally and postnatally (Barlow and Sullivan, 1982). In the rhesus monkey, the PCB content of tissues in nursing infants was directly related to maternal PCB levels in the fat (Barsotti and Van Miller, 1984). At weaning, the PCB concentration in infant fat can be 4-7 times that found in the mother.

In adult male mice, PCB in the diet greater than 100 ppm was associated with reduced sperm concentration. At 400 ppm PCB in the diet for 2 weeks, there were decreases in testicular and seminal vesicle weights, sperm concentrations, and total sperm number. A no-effect dose for testicular effects in the male mouse was around 50 ppm PCB in the diet, even though liver weight was significantly elevated. In female mice and monkeys chronic PCB exposure at doses corresponding to about 5 ppm in the diet (or 0.8 mg/kg body weight) caused prolongation of the estrus cycle. Ovulatory failure has been observed in female monkeys receiving PCB at 4 mg/kg body weight/day for 28 days.

Adverse effects on fertility in male rodents and monkeys were seen with PCB doses that produced symptoms of toxicity. Fertility in females appears to be more sensitive to PCB, although the type of PCB mixture employed is an important determinant of the degree of response.

Numerous studies have been conducted which involved administration of PCB during pregnancy to mice, rats, rabbits, pigs, dogs, and monkeys. In all species tested, PCB exposure is more often associated with low birth weights, and high perinatal and postnatal mortality, than with gross structural deformities. Doses required to produce adverse effects on the offspring were shown to vary for different PCB mixtures and different isomers. Neonatal exposure of rats and mice to PCB through the milk was reported to affect the subsequent reproductive capacity of males and females. Some of the adverse effects of PCB on pregnancy outcome have been seen at doses which do not produce overt signs of maternal toxicity. In particular infant monkeys exposed to PCB in utero and through nursing showed decreased birth weights and subsequent adverse effects on learning and behavior (Barsotti and Van Miller, 1984).

V. Organic Solvents

A. Aromatic Hydrocarbons

The common aromatic solvents - benzene, xylene, toluene - all produce a similar pattern of reproductive toxicity in animals. None of the compounds consistently produce embryolethal or teratogenic effects, even at doses which are maternally toxic. Significant fetotoxicity, however, has been observed at maternally toxic doses as well as with doses below those toxic to the mother.

One study reported that rats, guinea pigs, and rabbits inhaling benzene at 80 or 88 ppm in air for 30-40 weeks developed increased testicular weight and histological damage to the seminiferous epithelium of the testes (Barlow and Sullivan, 1982). Exposure of female rats to benzene in air at 1.6 or 9.4 ppm for four months had no effect on fertility, although inhalation of 210 ppm benzene starting 10-15 days before mating was reported to prevent pregnancy. Exposure of pregnant rats mice and rabbits to benzene has not provided evidence for production of gross teratogenic effects in studies that were well-designed. Fetotoxicity has been associated with exposure of pregnant rodents to benzene, however. Fetal body weights were reduced when pregnant rats inhaled 100 ppm benzene on days 6-15 of gestation (Coate et al., 1983). No maternal toxicity resulted from the benzene exposure. At lower benzene concentrations of 1, 10, and 40 ppm, no effects were seen on pregnant rats or their fetuses.

The teratogenic and fetotoxic potential of xylenes has been studied in pregnant mice following oral administration (Marks et al., 1982), and in mice and rats inhaling the solvent vapors (Shigeta et al., 1983; Ungvary et al., 1980, 1981; Barlow and Sullivan, 1982). In mice, a mixture of xylene isomers and ethylbenzene at doses up to 1.03 g/kg of body weight/day during gestation days 6-15 produced no effects on the mother or fetus. Higher doses (2.06-4.13 g/kg/day) caused maternal toxicity and death, teratogenic effects, and fetotoxicity. The three isomers of xylene have been studied individually in pregnant rats by inhalation of 35, 350, or 700 ppm in air. All of the isomers produced fetotoxicity (decreased fetal weight, delayed skeletal development). The p-xylene isomer appeared to be the most fetotoxic, causing embryolethality and retarded fetal development in the absence of maternal toxicity. No teratogenic effects were associated with any of the xylene isomers.

The reproductive toxicity of toluene has been evaluated by oral administration to pregnant mice and inhalation exposure of pregnant mice and rats (Litton Bionetics, 1978; Shigeta et al., 1982; Tatrai et al., 1980; Barlow and Sullivan, 1982). Similar to the effects of xylene and benzene, toluene does not appear to be teratogenic at doses which do not produce maternal toxicity or significant embryolethality. In pregnant mice given toluene orally at 0.26, 0.43, or 0.87 g/kg body weight on days 6-15 of gestation, embryolethality was noted in the absence of signs of maternal toxicity. In rats or mice inhaling toluene during pregnancy, exposures to 100 ppm in air had no effects on the mother or fetus. At

400 ppm in air and above, toluene produced signs of maternal toxicity, fetotoxicity (reduced fetal weights, retarded skeletal development) and embryolethality, but no clear evidence for structural malformations in the offspring.

B. Carbon Disulfide

Several studies have examined reproductive effects in male and female rats exposed to carbon disulfide (Council on Environmental Quality, 1981). Male rats receiving intraperitoneal injections of carbon disulfide at 78 mg/kg body weight every other day for 2 months showed decreased numbers of spermatozoa. Continuation of the treatment for 4 months caused testicular damage and inhibition of spermatogenesis. Adverse effects have been demonstrated in female rats inhaling as little as 4 ppm carbon disulfide before mating and during pregnancy. Effects included increased embryolethality, reduced fetal weight, and increased incidences of structural malformations in the offspring. At least one study conflicts with reports of carbon disulfide-induced teratogenicity.

Hardin and coworkers (1981) exposed pregnant rats and rabbits to carbon disulfide at 20 and 40 ppm in air throughout gestation. Their results indicated no evidence for teratogenic effects, fetotoxicity or maternal toxicity in either of the species tested.

C. Chlorinated Hydrocarbons

Several commercially important chlorinated hydrocarbons have been tested for reproductive effects in animals. These include methyl chloride, 1,2-dichloroethane (ethylene dichloride), 1,1,1-trichloroethane (methyl chloroform), trichloroethylene, tetrachloroethylene, and chloroform (trichloromethane). Evidence for teratogenicity by these compounds is limited, although all are capable of producing fetotoxic effects.

The National Institute for Occupational Safety and Health (NIOSH, 1984a) recently concluded that methyl chloride should be considered a possible teratogen. They cited the results of a study in which mice were exposed by inhalation at concentrations of 100, 250, 500, 750 or 1500 ppm methyl chloride on days 6-18 of gestation. At the 500 and 750 ppm exposure levels, fetal heart malformations were observed. The relationship of maternal toxicity to this teratogenic effect was not discussed. In addition to teratogenic effects, male rats inhaling 1000 ppm methyl chloride developed testicular degeneration. At 50 or 250 ppm in air, methyl chloride had no effects on male rats.

The reproductive effects of 1,2-dichloroethane were evaluated in a 2-generation study in male and female mice (Lane et al., 1982). Animals received drinking water containing 1,2-dichloroethane at a concentration of 30, 90, or 290 mg/ℓ (corresponding to a dose of 5, 15, or 50 mg/kg/day) for a minimum of six weeks prior to mating. No effects could be demonstrated in either generation on male or female fertility, litter survival and growth, dominant lethal mutations, or malformations in the offspring. Similar negative results were cited by Lane et al. (1982) for animals exposed to 1,2-dichloroethane by inhalation and incorporation in the diet.

In the same study in which 1,2-dichloroethane was evaluated for reproductive toxicity, Lane and coworkers (1982) also tested 1,1,1-trichloroethane for reproductive effects. Mice received 1,1,1-trichloroethane in the drinking water over two generations at a concentration of 580, 1750 or 5830 mg/ℓ, corresponding to a dose of 100, 300, or 1000 mg/kg body weight/day. As with 1,2-dichloroethane, no effect of 1,1,1-trichloroethane was seen on fertility, gestation, viability, lactation, survival of offspring, weight gain, malformations, or dominant lethal mutations. The negative findings of Lane and coworkers (1982) in this study were supported by similar results from earlier studies involving rats and mice inhaling 875 ppm of 1,1,1-trichloroethane on days 6-15 of gestation (Barlow and Sullivan, 1982).

The reproductive effects of trichloroethylene have been evaluated in rats exposed by inhalation and ingestion, and in mice exposed by inhalation. In one study, no adverse effects were found in rats or mice resulting from inhalation of 300 ppm trichloroethylene on days 6-15 of gestation (Barlow and Sullivan, 1982). In another report, however, fetotoxicity (retarded fetal development) resulted from exposure of rats to 100 ppm trichloroethane in air on days 8-21 of gestation (Healy et al., 1982). No gross structural malformations were observed. The longer period of trichloroethylene exposure in the Healy et al. (1982) study may have accounted for the different results obtained in comparison to the study with rats and mice inhaling 300 ppm. Oral exposure of female rats to trichloroethylene was shown to have no effect on fertility or pregnancy (Manson et al., 1984). Rats received trichloroethylene orally at 10, 100, or 1000 mg/kg body weight/day for two weeks prior to mating and throughout pregnancy. The only effect observed was decreased neonatal survival among rats from the 1000 mg/kg dose group, which was associated with significant maternal toxicity.

Pregnant rats and mice have been exposed to tetrachloroethylene by inhalation (Reichert, 1983; Barlow and Sullivan, 1982). Inhalation of 300 ppm tetrachloroethylene on days 6-15 of gestation resulted in fetotoxicity in mice but not in rats. There was no evidence for teratogenicity in either species. At higher exposure levels associated with maternal toxicity in pregnant rats (900-1000 ppm in air) tetrachloroethylene was reported to produce teratogenic effects and postnatal neurobehavioral disturbances.

The effects of chloroform on pregnancy in rodents has been rather thoroughly studied, although little is known regarding its effects on fertility in animals. Teratogenic effects and embryotoxicity have resulted from oral administration and inhalation of chloroform by pregnant rats (Ruddick et al., 1983; Barlow and

Sullivan, 1982). Most effects are associated with chloroform-induced maternal toxicity. There is limited evidence that exposure of rats to 30-100 ppm chloroform by inhalation during pregnancy results in teratogenic effects that occur in the absence of maternal toxicity.

D. Methyl Ethyl Ketone (MEK)

MEK is a widely used nonchlorinated solvent. Studies conducted by the Dow Chemical Company provided suggestive evidence of MEK teratogenicity in rats (Deacon et al., 1981; Barlow and Sullivan, 1982). Pregnant rats inhaled 400, 1000, or 3000 ppm MEK on days 6-15 of gestation. At 3000 ppm maternal weight gain was depressed, and in the offspring there was an increased incidence of skeletal alterations and a delay in the ossification of fetal bones. These fetal effects were considered by the authors to be minor malformations. In an earlier study of identical design, rats in the 3000 ppm dose group showed a significant increase in gross external malformations, in the absence of significant maternal toxicity.

E. Glycol Ethers

A large body of animal data was presented at the Symposium on Toxic Effects of Glycol Ethers, sponsored by the National Institute for Occupational Safety and Health on September 19-21, 1983. The proceedings of this symposium, containing several reports of reproductive toxicity testing, were published in volume 57 of Environmental Health Perspectives, August, 1984.

In general, the short-chain glycol ethers were shown to be both fetotoxic and teratogenic in rodents by various routes of exposure. In addition, specific adverse effects on testicular function have been demonstrated. The prototype chemical of the glycol ether class, 2-ethoxyethanol (ethylene glycol monoethyl ether), inhibited fertility in male and female mice, caused testicular atrophy and abnormal sperm in male rats and mice, and was teratogenic and fetoxic in mice, rats, and rabbits. Teratogenesis, fetal growth retardation, and embryolethality were demonstrated in rats and rabbits at dose levels below or similar to those producing maternal toxicity. Similar effects were reported for 2-methoxyethanol (ethylene glycol monomethyl ether) and ethylene glycol monoethyl ether acetate. For the higher ethylene glycol ethers, ethylene glycol monopropyl ether acetate and ethylene glycol monobutyl ether, maternal toxicity appeared to predominate over teratogenicity or fetotoxicity.

VI. Anesthetic Agents

Two widely used anesthetic gases, halothane and nitrous oxide, have been evaluated for reproductive toxicity in animals. In pregnant female rats inhaling halothane, several studies reported no adverse effects on fertility or the fetus (Council on Environmental Quality, 1981). One study with pregnant mice inhaling 10,000 or 15,000 ppm halothane 3 hours/day on days 12-15 of gestation reported an increased incidence of cleft palate and limb developmental defects. Embryolethality and fetotoxicity (decreased fetal weight and crown-rump length) was reported when pregnant hamsters inhaled a mixture of 60% nitrous oxide and 0.6% halothane on days 9-11 of gestation.

Studies with nitrous oxide administered by inhalation to pregnant rats provided evidence of fetotoxicity and embryolethality at concentrations as low as 100 ppm. In one well-designed study in which pregnant rats and rabbits inhaled 1000 ppm nitrous oxide on gestation days 1-19 (rats) or 1-24 (rabbits), no teratogenic effects, maternal toxicity or fetotoxicity were observed (Hardin et al., 1981). Reversible effects on spermatogenesis were reported when male rats inhaled 200,000 ppm nitrous oxide, 8 or 24 hours/day, for up to 35 days after birth (Council on Environmental Quality, 1981).

VII. Epichlorohydrin

The antifertility effects of epichlorohydrin on male rats is well documented. Reversible infertility in the absence of histologic damage to the gonads was first shown in male rats given epichlorohydrin orally at 15 mg/kg body weight for 12 days (Barlow and Sullivan, 1982). Higher doses caused damage to the testes which resulted in permanent sterility. Exposure of male rats to 50 ppm epichlorohydrin by inhalation for 10 weeks resulted in infertility that was reversed two weeks after removal from exposure (John et al., 1983). At a lower exposure level of 25 ppm, fertility was impaired but not abolished in male rats. An exposure level of 5 ppm epichlorohydrin in air had no effect on fertility in male rats. In male rabbits exposed to 5, 25, or 50 ppm epichlorohydrin in air, no effect on fertility could be seen. Similarly in female rats, inhalation of up to 50 ppm epichlorohydrin for 10 weeks caused no reduction in fertility.

Epichlorohydrin appears to have no specific adverse effects on the outcome of pregnancy. In pregnant rabbits inhaling epichlorohydrin at 2.5, 25, 50, or 100 ppm no effects were observed in the absence of maternal toxicity (Barlow and Sullivan, 1982). Among female rats inhaling 5, 25, or 50 ppm epichlorohydrin for 10 weeks prior to mating, no adverse effects were noted on the estrus cycle, pregnancy rate, or number and viability of the offspring (John et al., 1983).

VIII. Ethylene Dibromide (EDB)

Adverse effects of EDB on the male gonads have been demonstrated in the rat and the bull. Atrophy of the testes and secondary sex organs occurred in rats inhaling 89 ppm EDB for 10 weeks (Barlow and Sullivan, 1982). At this level of exposure, however, 20% of the animals died. At lower concentrations of EDB that were not significantly toxic (19 or 39 ppm), no specific effects on the gonads of male rats were seen. Calves and bulls were shown to be much more susceptible to a selective toxic action of EDB on the gonads. Daily oral doses of EDB averaging 2 mg/kg body weight/day resulted in semen and sperm abnormalities, and damage to the testes, which occurred in the absence of other signs of toxicity (Barlow and Sullivan, 1982). These effects were reversible, however.

The effect of inhalation exposure to EDB during pregnancy was studied in rats and mice. In one series of experiments, pregnant rats and mice inhaled EDB at 20, 32, 38, or 80 ppm on days 6-15 of pregnancy (Barlow and Sullivan, 1982). There was no apparent effect of EDB treatment on the incidence of major congenital malformations in the fetuses of rats or mice. Fetotoxicity was observed at doses which caused maternal toxicity. In one group of pregnant rats inhaling 32 ppm EDB, an increase in the incidence of minor congenital defects was observed in conjunction with slight maternal toxicity. Smith and Goldman (1983) exposed rats to EDB at levels of 0.43, 6.67, or 66.67 ppm in air during pregnancy. At the two higher dose levels maternal toxicity was evident, and the offspring showed signs of postnatal neurobehavioral impairment. No effects on the mother or fetus were evident from exposure to 0.43 ppm of EDB in air. Hardin and coworkers (1981) administered EDB by daily intraperitoneal injection at 55 mg/kg body weight to pregnant rats on days 1-15 of gestation. The EDB treatment produced signs of maternal toxicity (significant change in maternal organ weights) but no evidence of fetotoxicity or teratogenicity.

[illegible] Ethylene Oxide (ETO)

ETO has produced testicular damage and impaired fertility in rodents inhaling a toxic concentration (Barlow and Sullivan, 1982). Guinea pigs inhaling 357 ppm ETO for 25 weeks showed general growth depression and testicular degeneration. Decreased fertility and dominant lethal effects were found in rats following a single 4-hour exposure to 1000 ppm ETO in air. Exposure of male rats to 10, 33, or 100 ppm ETO in air for 12 weeks had no effect on fertility indices (Snellings et al., 1982a). A single intravenous injection of ETO at 25, 50, or 100 mg/kg body weight to male mice did not result in dominant lethal mutations when the animals were subsequently mated with untreated females (Barlow and Sullivan, 1982).

Several studies were conducted with female rats exposed to ETO before and during pregnancy. Exposure of pregnant rats to 10, 33, or 100 ppm ETO in air on days 6-15 of gestation resulted in fetotoxicity at the highest dose level, but no evidence of embryolethality or teratogenicity (Snellings et al., 1982b). Similar findings of fetotoxicity were reported by Hardin and coworkers (1983) in pregnant rats and rabbits inhaling 150 ppm ETO. Snellings and coworkers (1982b) exposed female rats to 10, 33, or 100 ppm ETO in air beginning 12 weeks before mating and continuing throughout pregnancy and lactation. Fertility was not affected in the ETO-exposed rats, although there were significantly fewer offspring born per litter in animals exposed to 100 ppm. Maternal toxicity did not result from the treatment, and survival and growth of offspring during the postnatal period were not adversely affected, even while the nursing mothers were exposed to ETO.

[illegible]. Formaldehyde

Data regarding the reproductive toxicity of formaldehyde in animals are limited. In male rats chronically exposed to formaldehyde at low doses (0.1 mg/ℓ in water, 0.4 ppm in air), no effects or fertility were seen (Barlow and Sullivan, 1982). Dominant lethal mutations were not produced by treatment of male mice with single intraperitoneal injections of formaldehyde at 15-40 mg/kg body weight. On the other hand, direct injection of 0.5 mℓ of a 4% solution of formaldehyde into the testes of monkeys resulted in complete sperm destruction in 60% of the treated animals (Lewis and Garcia, 1984).

Pregnant mice received formaldehyde orally at doses up to 185 mg/kg body weight/day on days 6-15 of gestation with no adverse effects resulting other than maternal toxicity (Barlow and Sullivan, 1982). Dogs were fed diets containing 125 or 375 ppm formaldehyde (corresponding to doses of 3.1 or 9.4 mg/kg/day) from days 4-56 after mating (Barlow and Sullivan, 1982). There was no evidence of embryolethality or teratogenicity, although fetal weights were slightly reduced in comparison to untreated control animals. Postnatal development of pups from formaldehyde-treated mothers appeared to be normal, and the pups were reported to have subsequently produced normal litters.

I. Vinyl Chloride

Several studies on the reproductive toxicity of vinyl chloride have been conducted in rodents. The absence of dominant lethal effects in male rats and mice inhaling vinyl chloride has been demonstrated with high dose short-term exposures (i.e., up to 30,000 ppm for 5 days) and lower dose subchronic exposures (i.e., 5000 ppm for 10 weeks or 1000 ppm for 11 weeks) (Barlow and Sullivan, 1982; Himeno et al., 1983). In addition, exposure of male rats or mice to vinyl chloride reportedly had no adverse effects on the sperm, testes, or secondary sex organs. Evidence was obtained, however, indicating that inhalation of 250 or 1000 ppm vinyl chloride for 11 weeks reduced the mating performance and fertility of male rats.

Pregnant rats, rabbits, and mice have been exposed to vinyl chloride at concentrations up to 2500 ppm in air. John and coworkers (1981) reported that maternal toxicity, but not fetotoxicity or teratogenicity, resulted from exposure of pregnant mice to 50 ppm or exposure of pregnant rats and rabbits to 2500 ppm vinyl chloride in air. In pregnant mice exposed to 500 ppm vinyl chloride in air, maternal toxicity, embryolethality and fetotoxicity all developed. One report indicated that embryolethality in the rat was increased by inhalation of 1500 ppm vinyl chloride early in pregnancy (days 1-9 of gestation) (Barlow and Sullivan, 1982).

XII. Hormones

The synthetic estrogen, diethylstilbestrol (DES), has well-documented reproductive effects in pregnant mice, rats, hamsters, rabbits, and monkeys (Council on Environmental Quality, 1981). In pregnant mice, daily subcutaneous injections of DES at doses ranging from 0.01 μg/kg to 10 mg/kg body weight/day during gestation caused severe developmental and functional disturbances in offspring of both sexes. In females, there was decreased fertility, sterility, and abnormalities of the genital tract; male offspring showed growth inhibition, sterility, and alterations of the reproductive tract. Similar effects were observed in the offspring of rats and hamsters treated with DES during pregnancy. Abnormalities of the genital tract were reported in female offspring of monkeys given DES orally at a dose of 1 mg/day from day 21, 100, or 130 of gestation to delivery.

High levels of corticosteroid hormones in early fetal life have been associated with developmental toxicity in animals. The synthetic glucocorticoid hormone, hydrocortisone acetate, has been studied for its ability to induce polycystic kidney disease (Crocker et al., 1983). The disease could be induced in the offspring of pregnant rats given an injection of 250 mg/kg body weight during the gestational period of fetal organ development. Polycystic kidney disease may also be induced by injecting newborn rats, rabbits, hamsters, and mice with the hormone, because kidney development continues postnatally in these species.

XIII. Acrylonitrile

Acrylonitrile is a commercially important chemical produced in large quantities in the United States. It is used to manufacture various resins, rubbers and acrylic fibers. Acrylonitrile has been given orally (10, 25, or 65 mg/kg) and by inhalation (40 or 80 ppm in air) to pregnant rats on days 6-15 of gestation (Lambotte-Vandepaer and Duverger-Van Bogaert, 1984, Barlow and Sullivan, 1982). By oral administration at 65 mg/kg/day, acrylonitrile produced maternal toxicity, fetotoxicity, embryolethality, and teratogenicity. At 25 mg/kg orally and at 80 ppm by inhalation, acrylonitrile also produced an increased incidence (not statistically significant) of the same types of fetal malformations as at the higher oral dose. The degree of maternal toxicity was apparently not correlated with the occurrence of gross fetal malformations and hence may not have accounted for the teratogenic effects observed. No effects were seen at oral doses of 10 mg/kg or inhalation of 40 ppm acrylonitrile in air. The teratogenicity of acrylonitrile in rats is supported by the results of a study in which pregnant hamsters were treated by intraperitoneal injection at 80-120 mg/kg body weight on day 8 of gestation (Willhite et al., 1981). In addition to maternal toxicity in the hamsters, major congenital malformations were observed. Injection of less than 80 mg/kg body weight to pregnant hamsters had no adverse effects on the mother or fetus.

XIV. Carbon Monoxide

Carbon monoxide has demonstrated adverse effects on the outcome of pregnancy in the mouse, rat, rabbit, sheep, pig, and monkey (Barlow and Sullivan, 1982). Carbon monoxide readily crosses the placenta, producing anoxia (lack of oxygen) in the fetus by reaction with fetal hemoglobin. The fetus is more sensitive to anoxia than the mother, and thus toxicity is observed at lower levels than in the mother.

The major effect from exposure to carbon monoxide during pregnancy is reduced fetal and postnatal weight gain and survival (Barlow and Sullivan, 1982). Effects are seen with exposure concentrations from around 90 ppm upwards, and are especially pronounced with exposures occurring late in pregnancy. Fetal and neonatal death can occur in the absence of effects on the mother. In addition to fetotoxicity, increased incidences of skeletal malformations in mice were observed with maternal exposures of 250 ppm continuously on days 6-15 of gestation. Major congenital malformations were reported when pregnant rabbits inhaled 180 ppm carbon monoxide on days 1-30 of gestation.

An important toxic effect of carbon monoxide on the fetus is impaired brain development. Damage to the brain can result in fetal or neonatal death, or may be expressed later in life through impaired learning and memory processes (Mactutus and Fechter, 1984).

~~XV~~ CHLOROPRENE

The results of studies with rats indicate that the reproductive effects of chloroprene may be dependent on the purity of the test material. When purified chloroprene was chronically administered by inhalation to male and female rats at concentrations up to 100 ppm in air, effects on fertility were not observed (Barlow and Sullivan, 1982). There was no evidence for the production of dominant lethal mutations in male rats exposed to chloroprene at levels up to 100 ppm in air. In Russian studies where the purity of chloroprene was not reported, dominant lethal effects were said to result from exposure to concentrations of 0.039-11 ppm in air.

Similarly, where the purity of chloroprene was not reported, Russian studies have indicated that exposure of pregnant rats to 1.1 ppm chloroprene in air was teratogenic and embryolethal (Barlow and Sullivan, 1982). Lower concentrations, down to 0.04 ppm in air, were reported to adversely affect postnatal survival and development. Other studies involving exposure to purified chloroprene at concentrations up to 25 ppm in air indicated no effect on the outcome of pregnancy in rats.

~~XVII.~~ 1,3-Butadiene

Limited evidence exists concerning the reproductive effects of 1,3-butadiene. The National Institute for Occupational Safety and Health (NIOSH, 1984b) summarized an unpublished study involving exposure of pregnant rats to 200, 1000 or 8000 ppm of 1,3-butadiene in air on days 6-15 of gestation. Maternal toxicity (depressed body weight gain) was evident at all exposure levels. Significantly retarded fetal growth was reported for the highest exposure group (8000 ppm) only. In addition, a significant increase in major skeletal abnormalities was observed in offspring of rats exposed to 8000 ppm 1,3-butadiene in air.

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